El consumo de guaraná (Paullinia cupana) mejora los parámetros hepáticos y renales en ratas diabéticas inducidas por aloxano

Guarana (Paullinia cupana) consumption improves hepatic and renal parameters in alloxan-induced diabetic rats

OR 2759

Guarana (*Paullinia cupana*) consumption improves hepatic and renal parameters in alloxan-induced diabetic rats

El consumo de guaraná (Paullinia cupana) mejora los parámetros hepáticos y renales en ratas diabéticas inducidas por aloxano

Renato de Souza Abboud[1], Ilma Cely de Amorim Ribeiro[1], Vivian Alves Pereira da Silva[1], Lanna Beatriz Neves Silva Corrêa[1], Gilson Telers Boaventura[2] and Maurício Alves Chagas[1]

[1]Laboratory of Cellular and Extracellular Biomorphology. Instituto Biomédico. Universidade Federal Fluminense. Niterói, Río de Janeiro. Brazil. [2]Laboratory of Experimental Nutrition. Faculdade de Nutrição. Federal Fluminense University. Niterói, Río de Janeiro. Brazil

Correspondence: Maurício Alves Chagas. Rua Professor Hernani Melo 101. 24210-130 Niterói, RJ, Brazil
e-mail: chagas.m@gmail.com

ABSTRACT

Introduction: diabetes mellitus is considered a chronic disease, characterized by the presence of high glycemic concentrations and dyslipidemia or hyperlipidemia caused by absence or deficiency of insulin secretion by pancreatic β-cells. Micro and macrovascular

complications may lead to nephropathy. Diabetic syndrome and oxidative damage are strongly related. The guarana plant (*Paullinia cupana*) has been described as an antioxidant agent.

Objective: this study aims to evaluate the protective action of the guarana compound on the biochemical profile of alloxan-induced diabetes in rats.

Method: twenty-eight male Wistar Furth rats were divided into four groups of seven animals each: the control group (CG) was fed a standard diet; the guarana group (GG) was fed a standard diet supplemented with guarana; the diabetic group (DG) included alloxan-induced diabetic rats fed a standard diet; and the diabetic guarana group (DGG) included alloxan-induced diabetic rats fed a standard diet supplemented with guarana. Induction was performed by intraperitoneal injection of alloxan 150 mg/kg.

Results: LDL (CG: 24.64 ± 2,59; GG: 38.93 ± 7.19; DG: 14.9 ± 3.96; DGG: 20.8 ± 4.04 mg/dL); HDL (CG: 14.8 ± 4.86; GG: 13 ± 1.41; DG: 22.5 ± 7.81; DGG: 30.66 ± 9.02 mg/dL); ALT (CG: 31.8 ± 4.81; GG: 22.16 ± 1.83; DG: 38 ± 1.4; DGG: 26.83 ± 2.13 U/L); AST (CG: 101.8 ± 5.07; GG: 117.5 ± 9.73; DG: 183.6 ± 4.21; DGG: 116.16 ± 12 U/L); Urea (CG: 51.4 ± 5.03; GG: 42.5 ± 8.24; DG: 129.16 ± 31.72; DGG: 150.5 ± 36.02 mg/dL); Creatinine (CG: 0.6 ± 0.12; GG: 0.53 ± 0.05; DG: 0.78 ± 0.11; DGG: 0.61 ± 0.07 mg/dL).

Conclusions: consumption of guarana (*Paullinia cupana)* by male Wistar Furth rats with alloxan induced diabetes without treatment had a beneficial effect on hepatic and renal function parameters, and raises the possibility of being used as supportive therapy in the treatment of diabetes.

Keywords: Diabetes mellitus. Guarana. Biochemical profile. Antioxidant. Alloxan.

RESUMEN

Introducción: la diabetes mellitus (DM) se considera una enfermedad crónica caracterizada por la presencia de altas concentraciones glucémicas, dislipidemia o hiperlipidemia causadas por ausencia o deficiencia de la secreción de insulina por las células β del páncreas. Sus complicaciones micro y macrovasculares pueden llevar a un cuadro de nefropatía. El síndrome diabético y el daño oxidativo están fuertemente relacionados. El guaraná (*Paullinia cupana*) se ha venido describiendo como un agente antioxidante.

Objetivo: este estudio tiene el objetivo de evaluar la posible acción protectora de este compuesto sobre el perfil bioquímico de ratas con diabetes inducida por aloxano. **Material y métodos:** veintiocho ratas macho Wistar Furth se dividieron en cuatro grupos de siete animales cada uno: el grupo de control (CG) se alimentó con la dieta estándar; el grupo de guaraná (GG) se alimentó con la dieta estándar complementada con guaraná; el grupo diabético (DG) se formó con ratas con diabetes inducida por aloxano que se alimentaron con la dieta estándar; el grupo diabético con guaraná (DGG) se formó con ratas con diabetes inducida por aloxano que se alimentaron con la dieta estándar complementada con guaraná. La inducción se realizó através de una inyección intraperitoneal de aloxano en dosis de 150 mg/kg.

Resultados: LDL (CG: 24,64 ± 2,59; GG: 38,93 ± 7,19; DG: 14,9 ± 3,96; DGG: 20,8 ± 4,04 mg/dl); HDL (CG: 14,8 ± 4,86; GG: 13 ± 1,41; DG: 22,5 ± 7,81; DGG: 30,66 ± 9,02 mg/dl); ALT (CG: 31,8 ± 4,81; GG: 22,16 ± 1,83; DG: 38 ± 1,4; DGG: 26,83 ± 2,13 U/L); AST (CG: 101,8 ± 5,07; GG: 117,5 ± 9,73; DG: 183,6 ± 4,21; DGG: 116,16 ± 12 U/L); urea (CG: 51,4 ± 5,03; GG: 42,5 ± 8,24; DG: 129,16 ± 31,72; DGG: 150,5 ± 36,02 mg/dl); creatinina (CG: 0,6 ± 0,12; GG: 0,53 ± 0,05; DG: 0,78 ± 0,11; DGG: 0,61 ± 0,07 mg/dl).

Conclusión: el consumo de guaraná (*Paullinia cupana*) por ratas Wistar con diabetes inducida por aloxano y sin tratamiento actuó de forma beneficiosa sobre los parámetros hepáticos y de función renal,

planteando la posibilidad de poder ser utilizado como terapia de soporte en el tratamiento de la diabetes.

Palabras clave: Diabetes mellitus. Guaraná. Perfil bioquímico. Antioxidante. Aloxano.

INTRODUCTION

Diabetes mellitus (DM) is considered a chronic disease, characterized by the presence of high glycemic concentrations, causing disturbances in lipid, carbohydrate and protein metabolism, which in turn are caused by the absence or deficiency of insulin secretion by pancreatic β-cells in pancreatic Langerhans islets (1). The hyperglycemia caused by diabetes may be controlled by exogenous insulin and other medicines. Yet, despite therapy, renal, vascular, ocular, skin, and peripheral nerve complications are common occurrences that reduce life span and quality for these patients (2).

Besides hyperglycemia, other symptoms, including dyslipidemia or hyperlipidemia, are involved in the development of the micro and macrovascular complications of diabetes, being the primary causes of diabetes-related morbidity and mortality (3). Diabetic nephropathy, a pathologic process secondary to microvascular damage, is the most common cause of terminal chronic kidney failure (TCKF) in patients under dialysis treatment in developed countries (30% of all cases) and Latin American countries (20% of all cases) (4). The presence of uremia and creatinemia in clinical lab examinations is an important marker for the evaluation of renal damage as caused by DM. The metabolization and excretion of urea, which results from proteolysis, as well as creatinine elimination as carried out by the urinary system, are jeopardized by the renal damage caused by hyperglycemia, which leads to the accumulation of these toxic metabolites within the organism (5).

The diabetic syndrome and oxidative damage are strongly interrelated. Diabetic hyperglycemia promotes the formation of reactive oxygen species (ROS), generated by reduction of one or two electrons from the oxygen molecule (O_2) (6,7). The cell damage caused by these free radicals may be irreversible, as they chronically accumulate in the body tissues. In this context, guarana (*Paullinia cupana*) has been described as an antioxidant agent possessing bioactive compounds that act directly on the body's metabolism, including methylxanthines, caffeine (8), theobromine (9,10), theophylline, tannins, saponins, catechins, epicatechins, and proantocianides (10-13). Caffeine is the main methylxanthine present in guarana extract (14), while polyphenols such as epicatechins and catechins are present in smaller concentrations, possessing a high biologic potential (15,16). Among the beneficial effects of polyphenols are the neutralizing effects of reactive oxygen species such as the superoxid anion and the hydroxyl radical, enzymatic activity, inhibition of cell proliferation, and antibiotic and anti-inflammatory effects (17,18). Saponins and tannins are found in high concentrations in guarana. These compounds, besides protecting DNA from damage (19), exert their antioxidant actions through inhibition of lipoperoxidation (20-22) .

Due to the potential risk of clinical and metabolic disturbances related to the increase in oxidative stress caused by diabetes mellitus, and considering the antioxidant action of guarana, this study aims to evaluate the possible protective action of this compound on the biochemical profile of alloxan-induced diabetes in rats.

METHODS AND EXPERIMENTS

Animals

The use of animals in this study was approved by the Ethics Committee for the Use of Animals at Universidade Federal Fluminense (CEUA–UFF), under approval number 972. Twenty-eight young male Wistar Furth rats (55 days of age) were enrolled for the experiment.

These animals were randomly divided into 4 experimental groups as follows: the control group (CG) was fed a standard diet; the guarana group (GG) was fed a standard diet supplemented with guarana; the diabetic group (DG) included alloxan-induced diabetic rats that were fed a standard diet; and the diabetic guarana group (DGG) included alloxan-induced diabetic rats that were fed a standard diet supplemented with guarana.

All animals were provided by the Nucleo de Animais de Laboratório (NAL/UFF) and placed in individual plastic cages at a temperature of 21-23 ºC with a relative humidity of 60%, light and darkness cycle control (12/12 h), and free consumption of water.

Alloxan-Induced Diabetes

The induction process was initiated with a feeding restriction over 30 hours in which the animals did not receive any kind of feeding except free water consumption. After the fasting period, the animals were manually contained and administered an intraperitoneal injection of alloxan monohydrate 98% (Cayman Chemical, code 9002196) previously diluted in a 0.9% sodium chloride solution in the proportion of 600 mg of alloxan in 40 mL of saline solution. This 1.5% solution was administered at a dose of 1 mL for every 100 grams of live weight through a 25 x 7 needle on the right inferior quadrant of the abdomen, with the animal duly contained. The rats were then put back in their cages with water and commercial rat feed *ad libitum (23)*.

The glycemia of all rats was measured three days after the administration of alloxan; following a fasting period of 6 hours, a drop of blood was obtained through a puncture with the aid of a scalpel on the animals' tail, and a OneTouch Ultra glucometer (Johnson & Johnson Company, USA) was employed to analyze the animals' glycemia. All animals presented glycemic levels equal to or higher than 270 mg/dL, hence they were considered to be diabetic and were included in the experiment (24). The animals remained under

experimentation in the bioterium for a period of eight weeks, and their glycemia, food consumption, and body weight were evaluated weekly. None of the animals died during the induction of diabetes or during the experimental period. No reversion cases were observed.

Experimental Feeds

The experimental feed was prepared at the Experimental Nutrition Laboratory at UFF (LabNE). A commercial pelletized feed was used (Nuvilab®, Nuvital, Paraná, Brazil) (Table I). To the experimental feed offered to the DGG and GG groups, 2 g of powdered guarana (*Paullinia cupana*) were added per kilogram of feed (25). The control group feed was also prepared from the same commercial pelletized feed, so that all animals received a standard diet. The ingredients were weighed and homogenized by an industrial mixer (Hobart®, São Paulo, SP, Brazil) with boiling water. The mass obtained was transformed into pellets and dried out in a ventilated oven (Fabbe-Primar® nº 171, São Paulo, SP, Brazil) at 60 ºC for 12 hours and, after identification, stored under refrigeration until its use.

Euthanasia of Animals and Collection of Biological Material

At the end of the experimental period at the bioterium, the animals were euthanized. The animals were anesthetized with 75 mg/kg of ketamine + 10 mg/kg of xylazine, and the previously calculated dose was intraperitoneally administered.

Once the anesthesia condition was achieved, as assessed by absence of the foot reflex, the animals were subjected to bleeding by an intracardiac puncture, from which 10 mL of blood were obtained. After bleeding, an additional dose of anesthesia was given, which led to the death of the animal. The blood samples collected were placed in serological flasks with separator gel, centrifuged at 3000 rpm for 15 minutes. The obtained serum was stored at -20 °C for the analysis of the biochemical profile.

Biochemical Profile

To assess the lipid profile, serum triglycerides, total cholesterol, high density lipoprotein (HDL), low density lipoprotein (LDL), and very low density lipoprotein (VLDL) levels were analyzed. Renal damage markers (total proteins, albumin, urea, creatinine) and hepatic enzymes alanine-aminotransferase (ALT) and aspartate-aminotransferase (AST) were also analyzed. These titrations were performed automatically using a Bioclin® analyzer (BioclinBS120, Quibasa – Química Básica Ltda., Belo Horizonte, MG, Brazil) in the Experimental Nutrition Laboratory at UFF (LabNE, Niterói, Brazil).

Statistical Analysis

The data were presented in the average and standard deviation form. To test the normal distribution of values, the Komolgorov-Smirnov test was employed. For the analysis of data, an ANOVA univariate test, in association with a multiple comparison test by Tukey-Kramer, was employed. Significance in all tests was established at the p < 0.05 level. The statistical analyses were made by the GraphPad Prism program in its 5.0, 2007 version (San Diego, CA, USA).

RESULTS

Of the 14 animals subjected to the intraperitoneal alloxan injection, 100% developed glycemic levels above 270 mg/dL, thus being considered diabetic and included in the experiment. The mean weight of the animals was lower in the diabetic groups (DG and DGG) when compared to the control groups (CG and GG), with an extremely significant difference between groups (p < 0.0001). The results are expressed in figure 1). Consumption in diabetic groups was higher when compared to the control groups (Fig. 2). The concentration of LDL cholesterol in the GG was 33.27% higher than that in the CG, 59.65% higher than in the DG, and 43.67% higher than in the DGG. The serum concentration of HDL cholesterol increased by 51.72% in

the DGG when compared to the CG, and by 57.59% when compared to the GG.

The serum levels of ALT increased by 30.31% in the CG when compared to the GG. In the DG, the concentration of ALT was 41.83% higher than in the GG, and 29.58% higher than that in the DGG. In relation to AST, the serum concentration in the DG was 44.55% higher than in the CG, 36% higher than in the GG, and 36.73% higher than in the DGG. The CG and GG did not present a significant difference in serum urea levels when compared to each other; however, when compared to the diabetic groups, the DG presented an increase of 60.20% when compared to the CG, and of 67.09% when compared to the GG; the DGG presented an increase of 65.84% when compared to the CG, and of 71.76% when compared to the GG.

The average serum creatinine levels did not present statistically significant differences between the CG and GG; the DG presented an increase of 23.07% as compared to the CG, and of 32.05% in relation to the GG. Yet, the DGG presented a decrease of 21.79% when compared to the DG and did not significantly differ from the CG. The remaining parameters of serum biochemistry did not exhibit any significant differences. The numeric data are expressed in table II.

DISCUSSION

The utilization of cytotoxic drugs aiming at a chemical induction of diabetes mellitus in Wistar rats for the production of experimental animal models is still largely employed (26,27). Nevertheless, the protocols utilized do not follow a single standard, presenting flaws in the establishment of the actual disease, reversion of the diabetic state, and post-induction death (26,28,29). During this work, it was observed that a 150 mg/kg dose of alloxan, at a 1.5% concentration, preceded by a fasting for 30 hours and applied by intraperitoneal injection, caused an increase in glycemia in 100% of the rats, and already within the first week. The animals evaluated presented a glycemia level equal to or higher than 270 mg/dL, and maintained this

glycemia along the eight weeks of the experiment without any induction-related deaths during this period. Such data certify the efficacy of this method of induction of diabetes mellitus in rats.

Differently from what happens in humans, diabetic rats are resistant to alterations in their lipidic profile (30). The results obtained in this work reinforce this hypothesis because, in the animals that had diabetes mellitus induced by alloxan, total cholesterol, VLDL cholesterol, and triglycerides did not present any statistically significant differences between the groups tested. Such effect is reinforced by Cardozo et al. (31), who found similar results after evaluating the serum levels of cholesterol, triglycerides, and glucose in rats with alloxan-induced diabetes.

The addition of guarana powder to the diet may improve the lipid profile of rats, as demonstrated by Ruchel et al. (32), who in their experiment revealed that this phytochemical could reduce LDL-cholesterol levels in hypercholesterolemic rats. Caffeine and the polyphenols present in guarana, similarly to the components found in green tea or coffee, can reduce the oxidation of LDL-cholesterol. This protecting effect of guarana makes it appear as an efficient nutraceutic in the reduction of cardiometabolic diseases (33). Nevertheless, in the supplemented animals evaluated in this research, the cholesterol fraction that changed was the one bound to HDL, with DGG mice presenting a significant increase when compared to the animals in the CG and GG. Such results are similar to those that were observed by Lerco et al. (30).

In animal models, we can evaluate acute hepatic damage, and both aminotransferases (ALT and AST) represent the indicators mainly used by researchers (34). Serum elevations of ALT and AST are observed when a pathologic process causes hepatic cell damage (35). In this study, in relation to ALT, a significant decrease in its serum levels was observed in the test groups, the ones that were supplemented with guarana added to their diet (GG and DG), when compared to the non-supplemented groups (CG and DG). The diabetic animals that

received guarana (DGG) also had a significant reduction in AST levels when compared to the diabetic control group. These results are in line with those of Kober et al. (36), who in their study evaluated the protective effect of guarana on hepatic damage in rats exposed to carbon tetrachloride, thus demonstrating the efficacy of guarana in the reduction of transaminases, by means of the stabilization of the hepatic cell membrane, which reduces the release of enzymes to the blood stream (35). The evaluation of the renal parameters showed a significant increase in the serum levels of urea in the animals of the diabetic groups when compared to the control groups, suggesting a possible picture of renal damage. Still, an analysis of the serum levels of creatinine in the tested groups showed that in the DGG serum creatinine was maintained near the CG value. An increase in the levels of urea in the DGG, without an increase in the levels of creatinine, may be linked to a greater protein intake in this group. According to Dalton (37), the titration of urea alone is nonspecific for a diagnosis of renal damage, since this parameter can undergo variations in its values because of the diet. In these cases, an assessment of both urea and creatinine will generate more reliable results (5).

CONCLUSION

We conclude that the consumption of guarana (*Paullinia cupana*) by Wistar rats with induced diabetes and without treatment acted in a beneficial way upon the hepatic and renal function parameters, and can therefore be used as supportive therapy in the treatment of diabetes.

REFERENCES

1. Kumar CR, Collins T. Patología Estructural y Funcional de Robbins. 6 ed. México DF: Mc Graw–Hill Interamericana; 2000.

2. Laher I. Diabetes and alpha lipoic acid. Frontiers in pharmacology 2011;2:69.

3. Taskinen MR. Diabetic dyslipidemia. Atherosclerosis Supplements 2002;3(1):47-51. DOI: 10.1016/S1567-5688(01)00006-X

4. Lopes L, Pereira M, Villar L, Moraes M. Diagnostico e tratamento da nefropatia diabética. In: Villar L, Castellar E, Moura E, et al. Endocrinologia Clínica Rio de Janeiro: Medsi 2001:625-36.

5. de Almeida ML, Saatkamp CJ, Barrinha A. Dosagens de ureia e creatinina em soro humano através da técnica de espectroscopia Raman comparada com o método bioquímico. São Paulo. 2014.

6. Çimen MB. Free radical metabolism in human erythrocytes. Clinica chimica acta 2008;390(1-2):1-11. DOI: 10.1016/j.cca.2007.12.025

7. Damasceno D, Souza M, Rudge M. Diabetes e malformações congênitas: estudos em animais e humanos. Metabólica 2006;8(6).

8. Tfouni SAV, Camargo MCR, Vitorino SHP, Menegário TF, Toledo MCdF. Contribuição do guaraná em pó (Paullinia cupana) como fonte de cafeína na dieta. Revista de Nutrição 2007;20:63-8. DOI: 10.1590/S1415-52732007000100007

9. Belliardo F, Martelli A, Valle MG. HPLC determination of caffeine and theophylline inPaullinia cupana Kunth (Guarana) and Cola spp. samples. Zeitschrift für Lebensmittel-Untersuchung und Forschung 1985;180(5):398-401. DOI: 10.1007/BF01027774

10. Salvadori MC, Rieser EM, Neto LMR, Nascimento ES. Determination of xanthines by high-performance liquid chromatography and thin-layer chromatography in horse urine after ingestion of guaraná powder. Analyst 1994;119(12):2701-3. DOI: 10.1039/AN9941902701

11.	Carlson M, Thompson RD. Liquid chromatographic determination of methylxanthines and catechins in herbal preparations containing guaraná. J AOAC Int 1998;81(4):691-701.

12.	Pelozo MIdG, Cardoso MLC, Mello JCPd. Spectrophotometric determination of tannins and caffeine in preparations from Paullinia cupana var. sorbilis. Brazilian Archives of Biology and Technology 2008;51:447-51.

13. Sombra LL, Gómez MR, Olsina R, Martínez LD, Silva MF. Comparative study between capillary electrophoresis and high performance liquid chromatography in 'guarana' based phytopharmaceuticals. Journal of Pharmaceutical and Biomedical Analysis 2005;36(5):989-94. DOI: 10.1016/j.jpba.2004.08.026

14. Baratloo A, Rouhipour A, Forouzanfar MM, Safari S, Amiri M, Negida A. The Role of Caffeine in Pain Management: A Brief Literature Review. Anesth Pain Med 2016;6(3):e33193-e. DOI: 10.5812/aapm.33193

15. da Silva GS, Canuto KM, Ribeiro PRV, et al. Chemical profiling of guarana seeds (Paullinia cupana) from different geographical origins using UPLC-QTOF-MS combined with chemometrics. Food Research International 2017;102:700-9. DOI: 10.1016/j.foodres.2017.09.055

16. Marques LLM, Panizzon GP, Aguiar BAA, et al. Guaraná (Paullinia cupana) seeds: Selective supercritical extraction of phenolic compounds. Food Chemistry 2016;212:703-11. DOI: 10.1016/j.foodchem.2016.06.028

17. Galleano M, Verstraeten SV, Oteiza PI, Fraga CG. Antioxidant actions of flavonoids: Thermodynamic and kinetic analysis. Archives of Biochemistry and Biophysics 2010;501(1):23-30. DOI: 10.1016/j.abb.2010.04.005

18.	Silva VAP, Boaventura GT, Abboud RS, Ribas JAS, Chagas MA. Consumption of Green Tea (Camellia sinensis) Improves

Lipid, Hepatic, and Hematological Profiles of Rats That Are Submitted to Long-Term Androgenic Stimulation. American Journal of Sports Science 2018;6(4):7.

19. Fukumasu H, Avanzo JL, Nagamine MK, Barbuto JA, Rao KV, Dagli MLZ. Paullinia cupana Mart var. sorbilis, guaraná, reduces cell proliferation and increases apoptosis of B16/F10 melanoma lung metastases in mice. Brazilian Journal of Medical and Biological Research 2008;41:305-10. DOI: 10.1590/S0100-879X2008000400008

20. Antonelli-Ushirobira TM, Kaneshima EN, Gabriel M, Audi EA, Marques LC, Mello JCP. Acute and subchronic toxicological evaluation of the semipurified extract of seeds of guaraná (Paullinia cupana) in rodents. Food and Chemical Toxicology 2010;48(7):1817-20. DOI: 10.1016/j.fct.2010.04.013

21. Mattei R, Dias RF, Espínola EB, Carlini EA, Barros SBM. Guarana (Paullinia cupana): toxic behavioral effects in laboratory animals and antioxidant activity in vitro. Journal of Ethnopharmacology 1998;60(2):111-6. DOI: 10.1016/S0378-8741(97)00141-4

22. Basile A, Ferrara L, Pezzo MD, Mele G, Sorbo S, Bassi P, et al. Antibacterial and antioxidant activities of ethanol extract from Paullinia cupana Mart. Journal of Ethnopharmacology. 2005;102(1):32-6. DOI: 10.1016/j.jep.2005.05.038

23. Oliveira GIVd. Monitoramento da indução do diabetes mellitus em ratos wistar com aloxana em diferentes doses. 2012.

24. Moustafa MH, Sharma RK, Thornton J, Mascha E, Abdel-Hafez MA, Thomas AJ Jr, et al. Relationship between ROS production, apoptosis and DNA denaturation in spermatozoa from patients examined for infertility. Human Reproduction 2004;19(1):129-38. DOI: 10.1093/humrep/deh024

25. Campos A, Barros A, Santos F, Rao V. Guarana (Paullinia cupana Mart.) offers protection against gastric lesions induced by ethanol and indomethacin in rats. Phytotherapy Research: An

International Journal Devoted to Pharmacological and Toxicological Evaluation of Natural Product Derivatives 2003;17(10):1199-202. DOI: 10.1002/ptr.1212

26. Ribeiro C, de Oliveira CAM, de Mello MAR. Exercício e prevenção do diabetes mellitus: importância do modelo experimental utilizando ratos Motriz Rio Claro 2007;13(1):6.

27. Zanoello AM, Melazzo-Mazzanti C, Gindri JK, Filapi A, Prestes D, Cecim M. Efeito Protetor do Syzygium cumini contra Diabetes Mellitus induzido por Aloxano em Ratos. Acta Farmacologica Bonaerense 2002;21(1):6.

28. Federiuk IF, Casey HM, Quinn MJ, Wood MD, Ward KW. Induction of Type-1 Diabetes Mellitus in Laboratory Rats by Use of Alloxan: Route of Administration, Pitfalls, and Insulin Treatment. Comparative Medicine 2004;54(3):252-7.

29. Negri G. Diabetes melito: plantas e princípios ativos naturais hipoglicemiantes. Brazilian Journal of Pharmaceutical Sciences 2005;41(2):22.

30. Lerco MM, Spadella CT, Machado JLM, Schellini SA, Padovani CR. Caracterização de um modelo experimental de Diabetes Mellitus, induzido pela aloxana em ratos. Estudo clínico e laboratorial. Acta Cirúrgica Brasileira 2003;18(2):11. DOI: 10.1590/S0102-86502003000200010

31. Cardoso S, Santos MS, Seiça R, Moreira PI. Cortical and hippocampal mitochondria bioenergetics and oxidative status during hyperglycemia and/or insulin-induced hypoglycemia. Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease 2010;1802(11):942-51. DOI: 10.1016/j.bbadis.2010.07.001

32. Ruchel JB, Braun JBS, Adefegha SA, Guedes Manzoni A, Abdalla FH, de Oliveira JS, et al. Guarana (Paullinia cupana) ameliorates memory impairment and modulates acetylcholinesterase activity in Poloxamer-407-induced hyperlipidemia in rat brain.

Physiology & Behavior 2017;168:11-9. DOI: 10.1016/j.physbeh.2016.10.003

33. Portella RdL, Barcelos RP, da Rosa EJF, Ribeiro EE, da Cruz IBM, Suleiman L, et al. Guaraná (Paullinia cupana Kunth) effects on LDL oxidation in elderly people: an in vitro and in vivo study. Lipids in Health and Disease 2013;12(1):12. DOI: 10.1186/1476-511X-12-12

34. Weber LWD, Boll M, Stampfl A. Hepatotoxicity and Mechanism of Action of Haloalkanes: Carbon Tetrachloride as a Toxicological Model. Critical Reviews in Toxicology 2003;33(2):105-36. DOI: 10.1080/713611034

35. Burtis CA, Bruns DE. Tietz Fundamentos de Química Clínica e Diagnóstico Molecular. 7 ed. Rio de Janeiro 2016.

36. Kober H, Tatsch E, Torbitz VD, Cargnin LP, Sangoi MB, Bochi GV, et al. Genoprotective and hepatoprotective effects of Guarana (Paullinia cupana Mart. var. sorbilis) on CCl4-induced liver damage in rats. Drug and Chemical Toxicology 2016;39(1):48-52. DOI: 10.3109/01480545.2015.1020546

37. Dalton RN. Creatinina sérica e taxa de filtração glomerular: percepção e realidade. Jornal Brasileiro de Patologia e Medicina Laboratorial 2011;47(1):4. DOI: 10.1590/S1676-24442011000100001

Table I. Nutritional composition of experimental feeds

Components*	Control (CG and DG)	Guarana (GG and DGG)
Humidity (max)	125 g/kg	125 g/kg
Net protein (min)	220 g/kg	220 g/kg
Ethereal extract (min)	40 g/kg	40 g/kg
Mineral matter (max)	90 g/kg	90 g/kg
Net fiber (max)	70 g/kg	70 g/kg
Calcium (min-max)	10-14 g/kg	10-14 g/kg
Phosphorus (min)	8,000 mg/kg	8,000 mg/kg
Guarana powder	0 mg/kg	2 mg/kg

*Composition of the commercial feed (Nuvilab®, Nuvital, Paraná, Brazil) used as base for experimental diets.

Table II. Biochemical analysis

Parameters	CG	GG	DG	DGG	p-value
Cholesterol (mg/mL)	47 ± 5.65 a	57.66 ± 12.61 a	48.83 ± 11.08 a	61 ± 15.16 a	< 0.2978
LDL (mg/mL)	24.64 ± 2.59 b	36.93 ± 7.19 a	14.9 ± 3.96 b	20.8 ± 4.04 b	< 0.0001
VLDL (mg/mL)	13.24 ± 4.08 a	8.2 ± 2.60 a	12.07 ± 3.08 a	14.53 ± 5.63 a	< 0.1655
HDL (mg/mL)	14.8 ± 4.86 a	13 ± 1.41 a	22.5 ± 7.81 a	30.66 ± 9.02 b	< 0.0005
Triglycerides (mg/mL)	66.2 ± 14.04 a	41 ± 13.00 a	65.33 ± 20.64 a	71 ± 21.31 a	< 0.0909
ALT (IU/L)	31.8 ± 4.8 a	22.16 ± 1.83 b	38 ± 1.41 c	26.83 ± 2.13 b	< 0.0001
AST (IU/L)	101.8 ± 5.07 b	117.5 ± 9.73 b	183.6 ± 4.21 a	116.16 ± 12 b	< 0.0001
Urea (mg/dL)	51.4 ± 5.03 b	42.5 ± 8.24 b	129.16 ± 31.72 a	150.5 ± 36.02 a	< 0.0001
Creatinine (mg/dL)	0.6 ± 0.12 b	0.53 ± 0.05 b	0.78 ± 0.11 a	0.61 ± 0.07 b	< 0.0006
Total proteins (g/dL)	5.12 ± 0.20 a	5.26 ± 0.25 a	4.83 ± 0.30 a	4.73 ± 0.47 a	< 0.05
Albumin (g/dL)	2.4 ± 0.14 a	2.35 ± 0.27 a	2.2 ± 0.38 a	2.13 ± 0.25 a	< 0.1268

The letters a, b and c next to the means represent the groups that showed statistically significant differences. The index for statistical significance in the test (one-way ANOVA) was $p < 0.05$. LDL: low density lipoprotein; VLDL: very low density lipoprotein; HDL: high density lipoprotein; ALT: alanine aminotransferase; AST: aspartate aminotranferase; CG: control group; GG: guarana group; DG: diabetic group; DGG: diabetic guarana group. Results are shown as mean ± standard deviation.
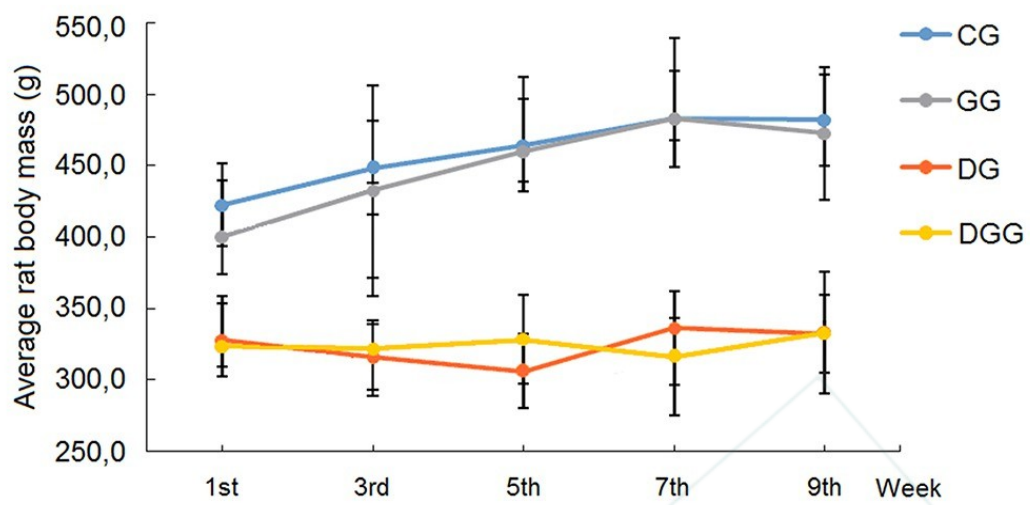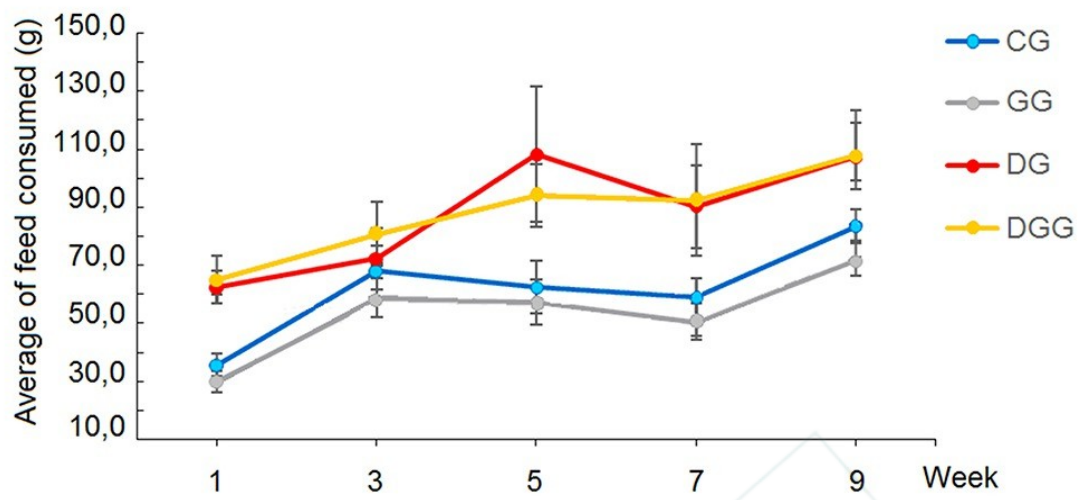
Fig. 1.

Fig. 2.