ISSN: 2230-9926

Available online at http://www.journalijdr.com

IJDR

International Journal of Development Research
Vol. 09, Issue, 11, pp. 31560-31565, November, 2019

RESEARCH ARTICLE OPEN ACCESS

ORAL SUPPLEMENTATION WITH *CAMPOMANESIA ADAMANTIUM* PEEL EXTRACT: EFFECT ON METABOLIC AND INFLAMMATORY PROFILES IN MICE

***[1]Amariles D.Ramires, [1]Elisvânia F. Santos, [1]Cacilda R. Hildebrand, [1]Jessica A. I. Muller, [1]Adriana C. G. Menezes, [2]Doroty M.Dourado, [1]Rodrigo J. Oliveira and [1]Andréia C. M. B. Antoniolli-Silva**

[1]Federal University of Mato Grosso do Sul (UFMS); Av. Costa e Silva, s.n.; Mato Grosso do Sul, 79070-900, Brazil
[2]University for Development of State and Region of Pantanal (Uniderp); R. Alexandre Herculano, 1400; Mato Grosso do Sul, 79035-470, Brazil

ARTICLE INFO

Article History:
Received 17th August, 2019
Received in revised form
26th September, 2019
Accepted 03rd October, 2019
Published online 30th November, 2019

Key Words:

Cerrado biome; Fruit peel; Antioxidant; Metabolic syndrome; Inflammation.

ABSTRACT

Campomanesia adamantium ("guavira") fruits exhibit pronounced antioxidant activity and are popularly used in the control of metabolic comorbidities, but no studies have evaluated this antioxidantproperty in the fruit peel.We evaluatedthe effect of the hydroethanolic extract of*C. adamantium* peel (ExCa) on the metabolic and inflammatory profilesof mice. Antioxidant activity was evaluated*in vitro*.The animals, fed a diet containing 65% starch, were grouped (*n*=8 each group) as follows: ExCa 250 (extract supplementation, 250mg/kg), ExCa500 (500mg/kg), and control (water supplementation). The experiment lasted 16 weeks.Supplementation was given by gavagefor the final four weeks. Body weight and dietary intake were measured. Blood was evaluated forinsulin, C-reactive protein, glucose, urea, creatinine, triglycerides, and inflammatory cytokines. Liver and kidneys were histologically examined. ExCaexhibited antioxidant potential, with high levels of phenolic compounds and tannins. Only supplementation with ExCaat 500 mg/kg reduced body weight, levels of glucose, triglycerides, total cholesterol, and hepatic steatosis, but thisregimen promotedkidney and liver inflammation.Inflammatory cytokines were not affected by extract. Supplementation withExCa showed potential utility as a nutritional strategy for the treatment of metabolic syndromecomorbidities.

Citation: Amariles D.Ramires, Elisvânia F. Santos, Cacilda R. Hildebrand *et al.* 2019. "Oral supplementation with Campomanesia adamantium peel extract: effect on metabolic and inflammatory profiles in mice", *International Journal of Development Research*, 09, (11), 31560-31565.

INTRODUCTION

Metabolic syndrome (MS) is a conditionwhich has been directly associated with chronic low-grade inflammation (Kaur, 2014) and consequently the adipose tissue, muscles and liver can become dysfunctional,exhibiting leukocyte infiltration,fibrosis,dysregulation of glucose and lipid metabolism(Hotamisligil, 2006; Minihane *et al*., 2015). Fruit trees native to the Cerrado biome have been increasingly investigated for the preventionand treatmentof MS and chronic low-gradeinflammation (Almeida *et al*., 2011). One of the promising fruits, is *Campomanesia adamantium* ("guavira") that is typically consumed fresh and as preserves, juices, and in ice-creams (Vallilo *et al*., 2006) and have been associated with reduced risk of obesity and associated processes (Donado-Pestana*et al*., 2018), including inflammation (Souza *et al*., 2017). Although typically discarded, plant parts such as peel, leaves, and seeds are not devoid of nutraceutical potential, representing sources of carotenoids, phenols, and phytosterols, compounds with health-promoting effects (Durante *et al*., 2017). Supplementation with essential oils from guavira seeds and peel has anti-inflammatory and analgesic effects on rodentsreceiving normal diet (Viscardi *et al*., 2017) and alsoreduces inflammation and platelet aggregation *in vitro* (Lescano *et al*., 2018).The seeds and peel may exhibit the same pharmacological properties as those observed in the fruits (Mendonça *et al*., 2006). To investigate the potential health benefits of *C. adamantium*fruit peel, we evaluated the effect of a hydroethanolic extract of this plant part on the metabolic and inflammatory profiles ofSwiss mice.

MATERIALSAND METHODS

Extract: Guavira fruits provided by the Agrarian Development and Rural Extension Agency (AGRAER) at Campo Grande, Mato Grosso do Sul state. Healthy fruits

weresanitized in water and manually pulped. The peelswere dried in an air circulating oven (40 °C), powdered and sieved (40 mesh), yielding 25%. Percolation was performed for 72 h (20 drops/min) to obtain the hydroethanolic extract (30:70, v:v). The extract thus produced was rotary-evaporated, freeze-dried, and stored in at –18 °C. For the*in vivo* assays, the freeze-dried extract was diluted in water to yield doses of 250 and 500 mg/kg (Souza *et al*., 2017).

Antioxidant activity and quantification of total phenols and tannins: Antioxidant activity was evaluated by applying the DPPH (a stable free radical) sequestration method (Brand-Williams *et al*., 1995) to extract concentrations ranging from 0 to 500 µM. Aliquots of 22 µL/well were transferred to 96-well plates containing 200 µL of DPPH (80% methanol solution) per well. The plates were covered, left in the dark at room temperature (22 °C) and read at 520 nm after30, 180, and 360 min. Assays were performed in triplicate. IC_{50} values,denoting the amount of extract required to decrease the initial DPPH concentration by 50%, were measured. Total phenol content was quantified using the Folin–Ciocalteu method, considering gallic acid as a standard.Tannins were quantified colorimetrically using Folin–Denis reagent, considering tannic acid as a standard.Readings were performed on a spectrophotometer at 760 nm. Ethanol was used as the blank and each point was determined in triplicate.Results were expressed as gallic acid equivalents (mgGAE/g) for total phenols and tannic acid equivalents (mgTAE/g) for tannins.

Sample: The experiment was performed on twenty-four60-day-old male mice (*Mus musculus*) under controlled laboratory conditions, in accordance with standards set out in the National Research Council's *Guide for the Care and Use of Laboratory Animals*. The study protocol was approved by the UFMS Ethics Committee on Animal Use (permit 848/2017).After 14-day acclimatization ona Nuvital standard diet, the animals were weighed and randomly assigned to three groups: ExCa 250 (diet supplemented with hydroethanolic extract of *C. adamantium*fruit peel at 250 mg/kg), ExCa 500 (extract supplementation at 500 mg/kg), and control (water supplementation). Except for supplementation, the same diets and water *ad libitum* were provided to all groups for 16 weeks. Supplementation (extract or water) was performed by gavage during the last four weeks of the experiment.

Experimental diet, weight gain and dietary intake measurements: The diet was prepared by Rhoster according to an experimental protocol of the American Institute of Nutrition (Table 1) and stored at 8 °C. The diet was selected to induce increased visceral fat, increased glycemic response, and damage to adipose and liver tissues (Hidebrand *et al*., 2017). Body weight of animals was measured at baseline and weekly throughout the experiment on a semi-analytical balance. Dietary intake was measured as grams of food per day.

Euthanasia andanalysis: Euthanasia, consisting of anesthesia with isoflurane overdose (3-5%)in an induction chamber, was followed by blood collection by posterior vena cava puncture. Blood serum was separated and total cholesterol, triglycerides, insulin, glucose, and urea were measured using a colorimetric-enzymatic method with commercial kits (LabTest) following the fabricant instructions. Creatinine and C-reactive protein were quantified using a colorimetric assay (Erhardt *et al*., 2004). Inflammatory cytokines IL-6, IL-10, IL-12, TNF, IFN-γ, and MCP-1 were quantified using a cytometricbead assaykit (BD Biosciences, lot 8171794) on a FACSCanto II flow cytometer.

Histopathological evaluation: Liver and kidney samples were processed and embedded in histological paraffin, and 5 µm–thick cross sections were obtained in rotary microtome (Microm, HM320). Sections were stained with hematoxylin-eosin (HE) and Masson's trichrome (TM).HE-stained liver and kidney slides were analyzed for tissue morphology. Liver slides were also examined (10 random fields) for the presence of steatosis and inflammatory foci. Steatosis and inflammatoryscoreswere determined based onKleiner *et al*., 2005. To detect fibrosis, liver slides were TM-stained and observed for the presence of collagen fibers.

Statistical analysis: Data were analyzed using Sigma Stat (Systat) and GraphPad Prism 5(GraphPad, USA) software, expressed as means ± standard error of the mean (SEM), and subjected to one-way ANOVA, followed by the Bonferroni test, with $p< 0.05$ indicating significant differences.

RESULTS AND DISCUSSION

Antioxidant activity and quantification of total phenols and tannins: *In vitro* antioxidant activity yielded an IC_{50} value of 980 µg/mL, revealing an antioxidant potential lower than that of other extracts from different parts of the same plant species—*e.g.*,an aqueous root extract with IC_{50}= 37.3 µg/mL (Espindola *et al*. 2016) and a methanolic extract fromfruit peel with IC_{50}= 163.70 µg/mL (Lescano *et al*., 2018).Total phenol content was 26.49 mgGAE/g being considered an intermediate quantity (Rufino *et al*., 2010) and higher than those reported for methanolic extracts from fruit peel, of 1.35 mgGAE/g (Lescano *et al*., 2018) and pulp,of 12.22 mgGAE/g (Alves *et al*., 2017). Tannin content was 3.70 mgTAE/g, higher than for fruits naturalized to the Cerradobiome, such as *Syzygiumcumini* (0.39 mgTAE/g) (Faria *et al*., 2011). Since phenolic compounds account for most of the antioxidant properties of plants (Jacobo-Velázquez and Cisneros-Zevallos, 2009), it can be inferred that the antioxidant activity is due to the phenols and tannins present in this plant part.

Table 1. Macronutrient composition of experimental diet.

Experimental diet	g/100 g
Protein	22
Lipid	5
Carbohydrate	65.00
Corn starch	*55.00*
Maltodextrin	*10.00*
Cellulose	5.00
Mineral mix	3.50
Vitamin mix	1.00
L-cystine	0.18
Choline bitartrate	0.25
Tert-butylhydroquinone	0.008
Total	101.94

***In vivo* assays:** Table 2 shows body weight and food intake values, and the ExCa 500 group reduced the body weight. Similar with our results, the leaves of other species in the genus, such as *C. xanthocarpa*, are popularly used for weight loss (Klafke *et al*., 2012) and reduced control weight gain in rats fed a high-calorie diet (Biavatti *et al*., 2004). But studies on the use of *Campomanesia*species forlosing weight have yielded contradictory results, given that Catelan *et al*. (2018)

Table 2. Body weight gain, food intake, and biochemical measurements in mice fed an experimental diet for 16 weeks supplemented with a hydroethanolic extract of *Campomanesia adamantium* fruit peel during the final four weeks

Parameters	Control (n = 8)	ExCa 250 (n = 8)	ExCa 500 (n = 8)
Weight and food			
Starting weight (g)	36.87±3.16	36.87±2.87	36.25±1.87
Final weight (g)	46.00±3.75	48.62±5.28	42.87±3.37
Weight gain (g)	9.12±1.87	11.75±2.94	6.62±1.97**
Food intake (g)	4.40±0.67	4.60±0.52	4.3±0.36
Biochemical parameters			
Blood glucose (mg/dL)	465.6±25.11	480.8±36.55	363.8±75.10*
Triglycerides (mg/dL)	176.8±17.85	183.6±23.98	157.00±66.70
Total cholesterol (mg/dL)	174.2±26.56	192.0±13.62	119.0±36.93*
Urea (mg/dL)	57.70±8.20	65.90±20.51	46.78±7.86
Creatinine (mg/dL)	0.28±0.03	0.30±0.12	0.20±0.10
Uric acid (mg/dL)	7.90±2.11	7.60±1.77	7.26±1.43
CRP (mg/dL)	0.24±0.12	0.21±0.07	0.21±0.08
Insulin (mU/L)	0.20±0.00	0.20±0.00	0.20±0.00

ExCa 250 and ExCa 500: supplementation with extract at 250 and at 500 mg/kg, respectively. Results expressed as means ± SEM (n = 8). ANOVA followed by Bonferroni test. * indicates significant differences (p< 0.05) relative to control in the same row; ** indicates significant difference (p< 0.01) relative to ExCa 250.

Table 3. Inflammatory cytokines in mice. Quantification by flow cytometry

Group	Cytokine (pg/mL)					
	IL-6	IL-10	IL-12	TFN	IFN-γ	MCP-1
Control	126.3±82.68	667.6±442.90	1267.0±841.40	12.9±3.71	63.6±40.88	111.4±62.38
ExCa 250	3.0±1.39	17.9±13.41	31.1±18.34	7.2±0.56	0.3±0.16	21.6±7.45
ExCa 500	0.7±0.12	0.0±0.00	32.1±31.81	5.9±0.90	2.5±1.54	9.9±3.06

Campomanesia adamantium peel extract supplementation at 250 mg/kg (ExCa 250) and at 500 mg/kg (ExCa 500). ANOVA followed by Bonferroni test, with p< 0.05 indicating significant differences.

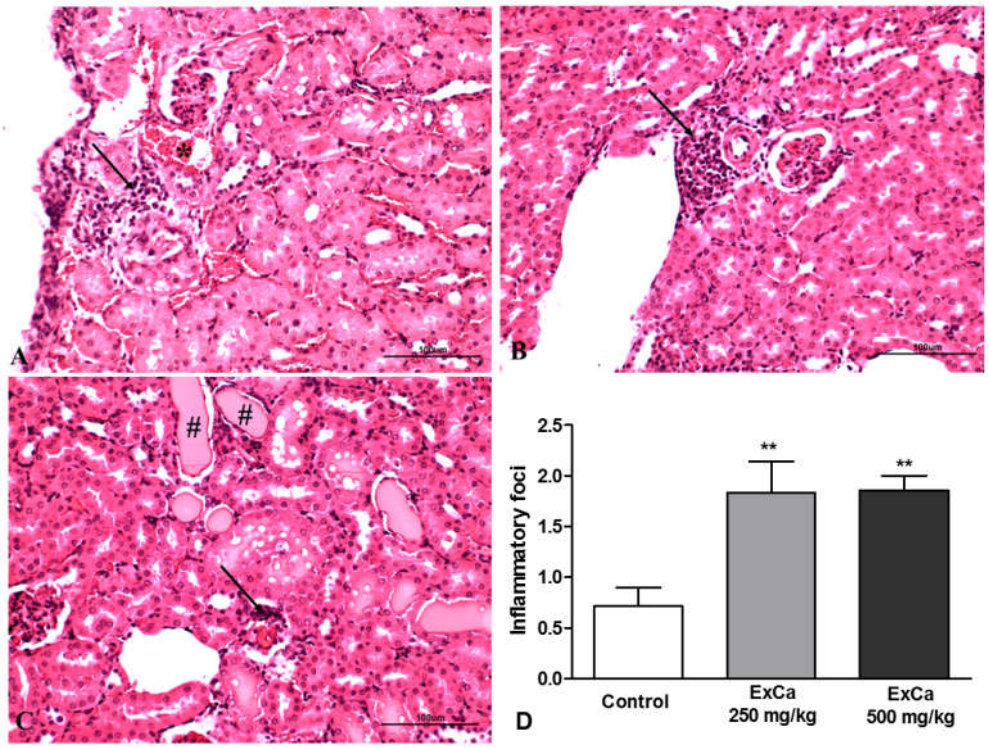

Figure 1. Inflammatory foci in mouse kidneys: control (A) and *Campomanesia adamantium* peel extract supplementation at 250 mg/kg (ExCa 250; B) and at 500 mg/kg (ExCa 500; C). Mononuclear inflammatory processes (arrows); hyperemia (*); proteinaceous deposition (#). Hematoxylin-eosin; 200×. Quantification of inflammatory foci (D). Results expressed as means ± SEM (n = 8); ANOVA followed by Bonferroni test, with p< 0.05 indicating significant differences. ** indicates p< 0.01 relative to control

and Boas *et al*. (2018), using leaf extract of *C. guazumifolia*and *C. pubescens*, respectively, did not found significant weight differencesbetween non-treated and treated mice. Serum glucose and total cholesterol levels were significantly lower (p< 0.05) in the ExCa 500 group. No differences among the groups were observed for the other variables evaluated (Table 2). Therefore, our results suggest the utility of ExCaas an alternative approach forglycemic control, crucial in the treatment of diabetes mellitus, another specie, *C. xanthocarpa*also demonstrated improvement in glycemia in rats (Biavatti *et al*., 2004). OnlyExCa 500 group exhibited reduced serum urea, showing levelssimilar with the referencerange of 45-53 mg/dL (Diniz *et al*., 2006). The hyperuricemia observed in another groups can result fromkidney disease that may be associated with several metabolic abnormalities linked with obesity, such as

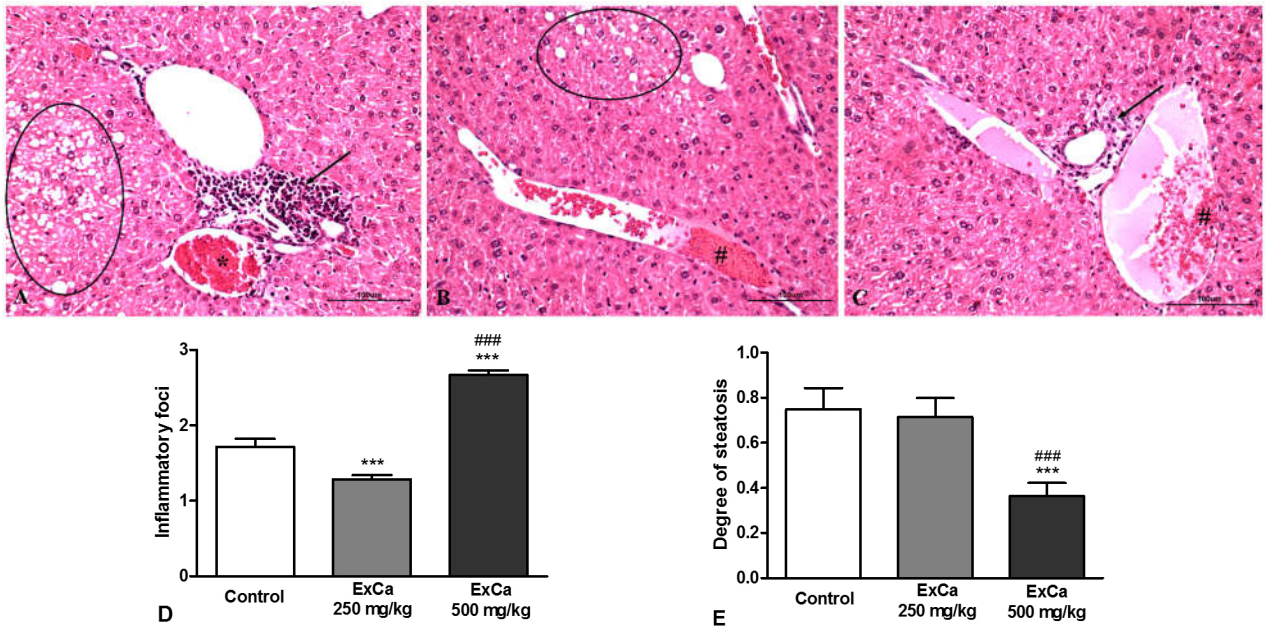

Figure 2. Inflammatory foci and steatosis in mouse livers: control (A) and *Campomanesia adamantium* peel extract supplementation at 250 mg/kg (ExCa 250; B) and at 500 mg/kg (ExCa 500; C). Mononuclear inflammatory processes (arrows); hyperemia (*); proteinaceous deposition (#), steatosis (circles). Hematoxylin-eosin; 200×. Quantification of inflammatory foci (D) and steatosis degree (E). Results expressed as means ± SEM (n = 8). ANOVA followed by Bonferroni test, with p< 0.05 indicating significant differences. * indicates p< 0.001 relative to control; ### indicates p< 0.001 relative to ExCa 250**

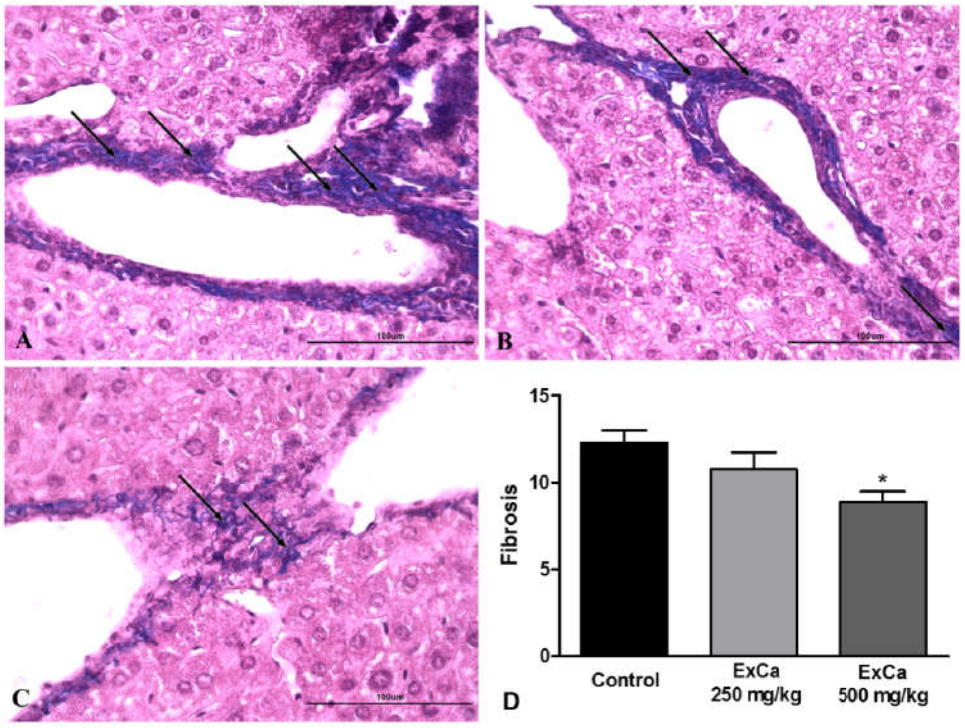

Figure 3. Fibrosis in mouse liver: control (A) and *Campomanesia adamantium* peel extract supplementation at 250 mg/kg (ExCa 250; B) and at 500 mg/kg (ExCa 500; C). Points of fibrosis (arrows). Masson's trichrome; 200×. Quantification of fibrosis (D). Results expressed as means ± SEM (n = 8). ANOVA followed by Bonferroni test with p< 0.05 indicating significant differences.
*** indicates p< 0.05 relative to control**

inflammation (Park *et al*., 2018). Another metabolic dysfunctionis the non-alcoholic fatty liver disease (NAFLD), characterized by the presence of inflammation, steatosis, and fibrosis (Chalasani *et al*., 2012). Inflammation can also affect other organs, including the kidneys (Declevesand Sharma, 2015). The inflammatory process was observed in our study in all groupsand had a marked presence of lymphocyte clusters.

The inflammation in kidney was more evident in the ExCa-supplemented groups, differingfrom control (p< 0.01) (Figure 1). In addition to inflammatory cells, hyperemia was detected in the control, whileproteinaceous deposition was found in both ExCa groups. Proteinaceous deposition can cause cell and tissue damage and are correlated with inflammatory process (Mareedu and Migrino, 2016).

Despite the occurrence of proteinaceous deposition and inflammation, Ex Casupplementation reduced hyperemia that is correlated with tissue damage (Moghadam *et al*., 2015). Similar with our results, *C. velutina*was found to induce inflammation and hemorrhage in rats given doses greater than 300 mg/kg (Araujo *et al*., 2017). However, Souza *et al*. (2017) observed no toxic effects on, or inflammation in, the kidneys of rats receiving normal diet and supplemented with guavira fruitpeel extract. These finding indicate thatdiet or animal type may have interfered with extract activity, inducing inflammation in mice with metabolic syndrome predisposition. Liver inflammatory foci were more numerous in the ExCa 500 group. ExCa 250 animals and control did not differ for foci (Figure 2D). Hyperemia was observed only in control and proteinaceous deposition occurred in all groups.The steatosiswas higher in control group and ExCa reduced hepatic steatosis levels, particularly the ExCa 500 group (Figure 2E).In addition to steatosis and inflammation, excess collagen (fibrosis) is also a characteristic feature of NAFLD (Xie *et al*., 2017).

In the present study, fibrotic spots were visualized on TM-stained slides from all groups, but supplementation with ExCaat 500 mg/kg reduced fibrosis occurrence (Figure 3). Steatosis- and fibrosis-reducing activitieshave been reported for *Phyllanthusniruri* extract (Zarzour *et al*., 2017), corroborating our results for ExCaat 500 mg/kg, although the anti-inflammatory effect found in the cited study was not observed in our assays. In a DPPH assay, *P. niruri* also exhibited antioxidant properties, reducing liver damage. Animal models of obesity and chronic low-grade inflammation have shownincreased expression of pro-inflammatory cytokines and macrophage influx (Stemmer *et al*., 2012; Mori *et al*., 2014; Martín *et al*., 2015). Although increased production of pro-inflammatory cytokines and decreased levels of anti-inflammatory cytokines have been observed elsewhere, no changes in IL-12, IL-10, IL-6, TNF, IFN-γ, or MCP-1 levels were detected in the present investigation (Table 3). So, these results indicated that the peels of guavira do not has activity in reduce mediators involved in inflammatory process induced by the experimental diet.

Conclusions

The hydroethanolic extract of *C. adamantium* fruit peel exhibited antioxidant potential. Used as dietary supplementation in mice, the extract reduced body weight, blood glucose, total cholesterol levels and liver steatosis, most markedly at 500 mg/kg—findings thatwarrant further investigation in animals with diabetes or coronary artery disease. However the peel extract does not showed anti-inflammatory activity.

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