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BIOMEDICAL SCIENCES

Hepato- and cardioprotective effects of *Baccharis trimera* (Less.) DC. against multiple risk factors for chronic noncommunicable diseases

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Abstract: Cardiovascular diseases are associated with high morbidity and mortality worldwide and have several risk factors, including dyslipidemia, smoking, and hypertension. Studies have evaluated isolated risk factors in experimental models of cardiovascular disease, but few preclinical studies have assessed associations between multiple risk factors. In the present study, hypertensive Wistar rats (Goldblatt 2K1C model) received a 0.5% cholesterol diet and were exposed to tobacco smoke for 8 weeks. During the last 4 weeks, the animals were treated with vehicle, an ethanol-soluble fraction of *B. trimera* (30, 100, and 300 mg/kg), or simvastatin + enalapril. A group of normotensive, non-dyslipidemic, and non-smoking rats was treated with vehicle. The levels of aspartate aminotransferase, alanine aminotransferase, urea, creatinine, and hepatic and fecal lipids, blood pressure, and mesenteric arterial bed reactivity were evaluated. Cardiac, hepatic, and renal histopathology and tecidual redox state were also investigated. Untreated animals exhibited significant changes in blood pressure, lipid profile, and biomarkers of heart, liver, and kidney damage. Treatment with *B. trimera* reversed these changes, with effects that were similar to simvastatin + enalapril. These findings suggest that *B. trimera* may be promising for the treatment of cardiovascular and hepatic disorders, especially disorders that are associated with multiple risk factors.

Key words: Asteraceae, Carqueja, dyslipidemia, herbal medicine, hypertension, smoking.

INTRODUCTION

Noncommunicable diseases, especially cardiovascular disease (CVD), are among the leading causes of mortality worldwide (World Health Organization 2011, Stanaway et al 2018). An estimated 17.9 million people died from cardiovascular disease in 2016, representing 31% of all deaths worldwide (Shahwan et al. 2019). Diabetes mellitus, hypertension, dyslipidemia, and smoking are the main aggravating risk factors for CVD (Yu et al 2009, DPhil et al. 2020).

According to the World Health Organization, approximately 1.13 billion people have hypertension worldwide, and it is the most prevalent chronic disease among noncommunicable diseases (World Health Organization 2019). Global cases of hypertension are expected to increase by 60% by 2025, with ~7.1 million deaths annually (Mills et al. 2016, Oliveira et al. 2019). Hypertension is a multifactorial and polygenic disease that involves complex interactions between homeostatic control mechanisms and environmental factors. It is

considered a worldwide public health problem and an important risk factor for cardiovascular complications, including atherosclerosis, stroke, and heart failure (Kunes & Zicha 2009, Carey et al. 2018). Evidence suggests that dyslipidemia contributes to the progression of hypertension by activating the renin-angiotensin system, reducing the availability of nitric oxide, causing endothelial dysfunction, and increasing salt sensitivity, vasoactive substance secretion, and cholesterol-rich cell membranes (Sposito 2004, Tran et al. 2020).

Dyslipidemias are characterized by elevations of low-density lipoprotein cholesterol (LDL-C) levels, reductions of high-density lipoprotein cholesterol (HDL-C), and elevations of triglyceride levels (Jama 2001). These changes increase the risk of CVD and likelihood of dying from coronary events. The rise in LDL is also closely related to the pathogenesis of nonalcoholic fatty liver disease (NAFLD), a disease that is emerging as the most common cause of chronic liver disease worldwide, the incidence of which is likely to continue to increase in the coming decades (Bellentani & Marino 2009, Diehl et al. 2019). Nonalcoholic fatty liver disease is characterized by the accumulation of lipids, especially triglycerides, in the liver. Lipid elevations result in an increase in liver enzymes and alterations of liver enzyme function, which may progress to steatohepatitis and cellular hepatocarcinoma (Fest et al. 2004, Pei et al. 2020). Nonalcoholic fatty liver disease is also considered an independent determinant of CVD. In addition to occurring in individuals who already have multiple cardiovascular risk factors, the relationship between NAFLD and CVD can lead to a higher risk of undesirable outcomes in this patient group. Nonalcoholic fatty liver disease is a complex problem with implications far beyond the liver (Targher et al. 2010, Lim et al. 2018).

In addition to hypertension and dyslipidemia, accumulating evidence indicates that tobacco smoking can negatively impact the incidence, severity, and clinical course of various types of chronic liver disease, directly contributing to a complex set of pathological interactions (El-zayadi 2006, Barbosa et al. 2020, Rutledge & Asgharpour 2020). Smoking causes tissue hypoxemia through an increase in carboxyhemoglobin. Hypoxemia, in turn, stimulates the production of erythropoietin, resulting in an increase of erythropoiesis. This effect induces the synthesis and degradation of hemoglobin and consequently alters iron metabolism, resulting in an increase in iron deposition in the liver, inflammation, and fibrosis (Bataller 2006, El-Zayadi 2006, Rutledge & Asgharpour 2020). Smoking is another risk factor for CVD, causing 45% of deaths in men under 65 years of age and more than 20% of deaths in men over 65. Men in the 45-54 age group who smoke are three times more likely to have a heart attack than non-smokers. In women, smoking accounts for approximately 40% of CVD-related deaths before age 65 (Mouhamad et al. 2006, Erhardt 2009). In addition to increasing mortality, smoking can lead to heart attacks through an increase in LDL-C levels and decrease in HDL-C levels, thereby increasing adhesion and fibrinogen molecules in the endothelium and stimulating platelet aggregation and vasoconstriction (Neki 2002, Lichtenstein et al. 2006, Labenz et al. 2019).

The prevention and control of hypertension and dyslipidemia using newly developed strategies that can accurately identify the interaction between multiple CVD and hepatic risk factors would be beneficial for both patients and society (Egan 2013, Vesa et al. 2020). One promising medicinal plant for the treatment of hepatic and cardiovascular diseases is *Baccharis trimera* (Less.) DC. (Asteraceae), popularly known

as carqueja. This species is common in southern Brazil, Argentina, Colombia, Chile, and Mexico. An infusion that is obtained from the leaves of this plant is popularly used to treat diabetes, digestive problems, and liver diseases (Kaut et al. 2018, Sabir et al. 2017, Oliveira et al. 2004).

Preclinical studies of *B. trimera* reported hypocholesterolemic, antiinflammatory, antiulcerogenic, antifungal, antibacterial, antiallergic, and anticarcinogenic activity (Alonso 1998, Lívero et al. 2016a, Lima et al. 2017, Rabelo et al. 2018). *B. trimera* also decreases adipogenesis and has antioxidant activity that can reduce lipid peroxidation, endothelial dysfunction, and cholesterol oxidation, a limiting step in the development of atherosclerosis (Pádua et al. 2010, Hurrell et al. 2015, Sabir et al. 2017, Nascimento et al. 2017). Hypoglycemic effects of *B. trimera* have also been reported (Coelho et al. 2004, Lívero et al. 2016b, Cosenza et al. 2019), in addition to vasorelaxant activity in rat aortic rings (Gómez et al. 2016). The most scientifically corroborated effect of *B. trimera* is hepatoprotective activity against liver injury that is caused by multiple risk factors (Lívero et al. 2016a, Rabelo et al. 2017, Barbosa et al. 2020). An increase in hepatocyte proliferation was previously found in rats after partial hepatectomy (Lima et al. 2017).

Despite the important preclinical therapeutic actions of *B. trimera* against dyslipidemia, no studies have simultaneously investigated the effects of this medicinal species on multiple risk factors that are associated with cardiovascular and hepatic disease. The present study employed a preclinical model of dyslipidemia, hypertension, and tobacco smoking and evaluated the cardio- and hepatoprotective effects *B. trimera*.

MATERIALS AND METHODS

Plant material and extract preparation

Aerial parts of *Baccharis trimera* were collected in February 2018 at the Paranaense University Medicinal Garden (S23°46'11.3"–W53°16'41.2"). The plant was identified by a botanic and the exsiccate are deposited at Paranaense University Medicinal Garden (voucher specimen no. 07). The plant was dried, crushed, and subjected to an extraction process. For this, 100 g the material was pulverized in a knife mill until granulometry of 850 µm and was submitted to an extraction process by infusing with 1 L of boiling water, until the extraction medium reached room temperature (24 hours). After filtration with filter paper to separate the residue, 100 mL of supernatant was treated with 300 ml of ethanol, for 36 h, for the precipitation of proteins and polysaccharides (Souza et al. 2020). The supernatant was then concentrated and lyophilized, giving rise to the ethanol-soluble fraction of *B. trimera* that was used in the experiments. The extract yield was 16.88%. Phytochemical characterization was performed using ultra-performance liquid chromatography (Acquity, Waters) coupled with high-resolution mass spectrometry (Xevo, Waters). The phytochemical characterization results were previously reported by Souza et al. (2020).

Animals

Forty-eight female Wistar rats, weighing 200-250 g, were obtained from the Federal University of Grande Dourados. The animals were housed in the Laboratory of Preclinical Research of Natural Products at Paranaense University with free access to filtered water and a solid diet under controlled environmental conditions (20° ± 2°C temperature, 50% ± 10% relative humidity; 12 h/12 h light/dark cycle) with environmental enrichment. The experimental protocol was

approved by the Paranaense University Animal Use Ethics Committee (protocol no. 32285/2017) and national and international guidelines regarding animal welfare and reduction of the number of animals used.

Experimental design

To induce renovascular hypertension, the animals were intramuscularly anesthetized with a combination of 50 mg/kg ketamine and 10 mg/kg xylazine and then underwent median laparotomy to expose the aorta and branches of the renal artery. The left renal artery was dissected for the placement of a silver clip (7 mm x 1 mm, 0.35 mm opening). The clip was closed at its distal end to induce unilateral renal ischemia (Schaedler et al. 2018). The abdominal cavity was then closed with continuous sutures (#10 cotton thread). After the surgical procedure, all of the animals received meloxicam (0.4 mg/kg, by gavage) every 24 h for 3 days to control postoperative pain. At the end of 4 weeks, animals with systolic blood pressure > 140 mm Hg were considered hypertensive.

To induce dyslipidemia, hypertensive animals received a standard commercial diet for rodents (Purina) that was enriched with 0.5% cholesterol. For this, 116 chicken egg yolks were mixed with 43 mL of corn oil and water (enough to bind) with 5kg of crushed rodent feed. The feed pellets were made manually with the aid of a sausage bagging machine and were dried in an oven at 50ºC, for 36 hours (Souza et al. 2020). The animals were exposed to the inhalation of filtered air or smoke from nine commercial tobacco cigarettes (0.8 mg nicotine, 10 mg tar, and 10 mg carbon monoxide) for 1 h daily, 5 days weekly, for 8 weeks (Souza et al 2020). Throughout the experiment period, food intake and body weight were monitored. During the last four experimental weeks, the animals were randomly assigned to six groups (n = 8/group) and orally treated by gavage with vehicle (0.1 mL of filtered water/100 g body weight; negative control [C–] group), *Baccharis trimera* extract (30, 100, and 300 mg/kg), or enalapril (15 mg/kg) plus simvastatin (2.5 mg/kg). Normotensive, non-dyslipidemic, and non-smoke-exposed rats were treated with vehicle (filtered water) and served as the basal group (n = 8). The doses of *B. trimera* were chosen according to previous study with this species in cardiovascular disease model (Barbosa et al. 2020, Souza et al. 2020).

Evaluation of cardiovascular parameters

Heart rate and blood pressure measurements

On the last day of the experimental period, the rats were intramuscularly anesthetized with ketamine (100 mg/kg) plus xylazine (20 mg/kg). A bolus injection of heparin (15 IU) was administered subcutaneously. The left carotid artery was isolated, cannulated, and connected to a pressure transducer that was coupled to a PowerLab recording system. Chart 4.1 software (ADI Instruments, Castle Hill, Australia) was used to record heart rate, systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure (MAP). After 15 min of stabilization, changes in heart rate and blood pressure were recorded for 5 min.

Vascular reactivity

After the blood pressure measurements, the rats underwent laparotomy. Mesenteric vascular beds (MVBs) were isolated and prepared for perfusion according to previously described methods (Schaedler et al. 2018). The MVBs were placed in a water-jacketed organ bath and perfused with physiologic saline solution (PSS; composition: 119 mM NaCl, 4.7 mM KCl, 2.4 mM $CaCl_2$, 1.2 mM $MgSO_4$, 25.0 mM $NaHCO_3$, 1.2 mM KH_2PO_4, 11.1 mM dextrose, and 0.03 mM

ethylenediaminetetraacetic acid) at 37ºC at a rate of 4 ml/min with 95% O_2/5% CO_2. Changes in perfusion pressure (mm Hg) were detected by a pressure transducer that was coupled to a PowerLab recording system using Chart 4.1 software (ADI Instruments, Castle Hill, Australia). After a 30-min equilibration period, the integrity of MVBs was evaluated by a bolus injection of 120 mmol KCl. A phenylephrine (3, 10, and 30 nmol; 50-100 µL) dose-response curve was then generated. After 30 min, the MVBs were continuously perfused with PSS plus phenylephrine (3 µM) to induce a prolonged increase in perfusion pressure. Under these conditions, vascular reactivity to acetylcholine (10, 30, and 100 pmol; 50-100 µL) was evaluated. A 15-min equilibration period elapsed between each drug administration.

Sample collection

After the cardiovascular evaluations, blood samples were collected from the left carotid artery using heparinized syringes. Plasma was separated by centrifugation at 1,500 x g for 10 min and stored at -80ºC for the biochemical analyses. The rats were then euthanized by puncture of the diaphragm while under anesthesia, and the heart, liver, and kidneys were removed. Samples were rapidly separated and frozen in liquid nitrogen to evaluate oxidative stress and perform biochemical analyses. Other organ samples were stored in 10% formalin solution for further histological analysis. Feces (representative of 2 days of feces accumulation) were collected directly from the animal cages on the last day of the experiment and stored at -20ºC until processing.

Biochemical analysis

Alanine aminotransferase (ALT), aspartate aminotransferase (AST), cholesterol, triglycerides, albumin, globulin, creatinine, and urea were evaluated in plasma using commercial kits and an automated analyzer (Roche Cobas Integra 400 plus).

Measurement of hepatic and fecal cholesterol and triglycerides

Lyophilized liver and fecal samples underwent lipid extraction using the gravimetric method that was described by Lívero et al. (2016a). Liver and fecal samples (200 mg) were mixed with 1.8 mL of hexane as the solvent and heated at 80ºC. After 12 h, the supernatant was transferred to a second flask and naturally evaporated. This procedure was repeated three times. To calculate the percentage of lipids in the liver, we used the following formula: Lipids (%) = 100 x [(final flask weight - initial flask weight)/0.1 g]

The lipid content was then weighed and suspended in 1 ml of chloroform plus 2 ml of isopropanol to determine hepatic and fecal levels of triglycerides and cholesterol using commercial kits in an automated analyzer (Roche Cobas Integra 400 plus).

Investigation of antioxidant system (heart, liver, and kidneys)

To investigate the antioxidant system, the heart, liver, and kidney samples were homogenized in a 1:10 dilution of potassium phosphate buffer (0.1 M, pH 6.5). Afterward, 100 µL was separated, suspended in 80 µL of trichloroacetic acid (12.5%), vortexed, and centrifuged at 6000 rotations per minute (rpm) for 15 min at 4ºC for the analysis of reduced glutathione (GSH) levels according to Sedlak & Lindsay (1968). The remaining homogenate was centrifuged at 9700 rpm for 20 min at 4ºC for the determination of superoxide dismutase (SOD) activity and lipoperoxidation (LPO) levels according to Gao et al. (1998) and Jiang et al. (1992), respectively.

Histopathological analysis of the heart, liver, and kidneys

Samples of the heart, liver, and kidney were fixed in buffered 10% formalin solution (distilled water, 35-40% formaldehyde, and monobasic and dibasic sodium phosphate), dehydrated with alcohol and xylene, embedded in paraffin, sectioned at 6 µm, and stained with hematoxylin/eosin. The slides were analyzed by optical microscopy (Leica DM 2500) to evaluate cellular alterations. Myocardial lesions were classified according to Acikel et al. (2005) into the following grades to compose a histological scale: 0 (absence of lesions), 1 (mild; focal myocyte damage or small multifocal degeneration with a slight degree of an inflammatory process), 2 (moderate; extensive myofibrillar degeneration and/or a diffuse inflammatory process), 3 (enhanced; diffuse inflammatory process and necrosis), and 4 (fibrosis). Hepatic lesions were classified as the following: 0 (0%; absence of lesions), 0.5 (1-5%; minor lesions), 1 (6-33%; moderate lesions), 2 (34-66%; marked lesions), and 3 (67-100%; massive lesions). Renal changes were analyzed according to the compartment where the lesion was located: 1 (glomeruli; basement membrane, cells, mesangial matrix), 2 (tubules), 3 (interstitium), and 4 (vessels). Lesions were classified according to their intensity as absent (0%), discrete (1-25%), moderate (26-50%), and severe (> 50%). The extent of lesions was classified as focal (< 50% of parenchyma) or diffuse (> 50% of parenchyma) according to Tumlin et al. (2007).

Statistical analysis

The data were analyzed for homogeneity of variance and a normal distribution. Differences between means were determined by one-way analysis of variance (ANOVA) followed by the Newman-Keuls *post hoc* test or by the Kruskal-Wallis test followed by Dunn's *post hoc* test. The level of significance was set at 95% ($p < 0.05$). The data are expressed as the mean ± standard error of the mean (SEM).

RESULTS

Hemodynamic effects of *Baccharis trimera*

No changes in heart rate were observed between any of the experimental groups (Fig. 1a). Increases in SBP (Fig. 2b), DBP (Fig. 1c) and MAP (Fig. 2d) were found in the negative control group compared with the basal group (113.90 ± 2.05, 73.03 ± 3.14, and 85.88 ± 1.94 mm Hg, respectively). Treatment with *B. trimera* (30 mg/kg) and simvastatin + enalapril reversed these changes. Treatment with 100 and 300 mg/kg *B. trimera* partially reversed these changes (Fig. 1).

With regard to vascular reactivity, the phenylephrine infusion increased perfusion pressure in the C– group (Fig. 2a). The infusion of acetylcholine decreased perfusion pressure in the same group (Fig. 2b). Treatment with 30 and 100 mg/kg *B. trimera* and simvastatin + enalapril restored vascular reactivity in MVBs. Treatment with 300 mg/kg *B. trimera* partially reversed the alterations of prefusion pressure that were induced by phenylephrine and acetylcholine (Fig. 2).

Effects of *Baccharis trimera* on biochemical profile

Hypertension, dyslipidemia, and smoking increased ALT and AST levels by 258.23% and 352.21%, respectively, compared with the basal group (27.75 ± 0.49 and 33.90 ± 2.03 U/L, respectively). Treatment with 30 mg/kg *B. trimera* completely reversed the increase in ALT and AST levels and restored urea and creatinine levels that were altered by these risk factors (basal group: 28.74 ± 0.63 and 0.35 ± 0.001 mg/dL, respectively). Furthermore, these risk factors increased albumin by 36.93% compared with the

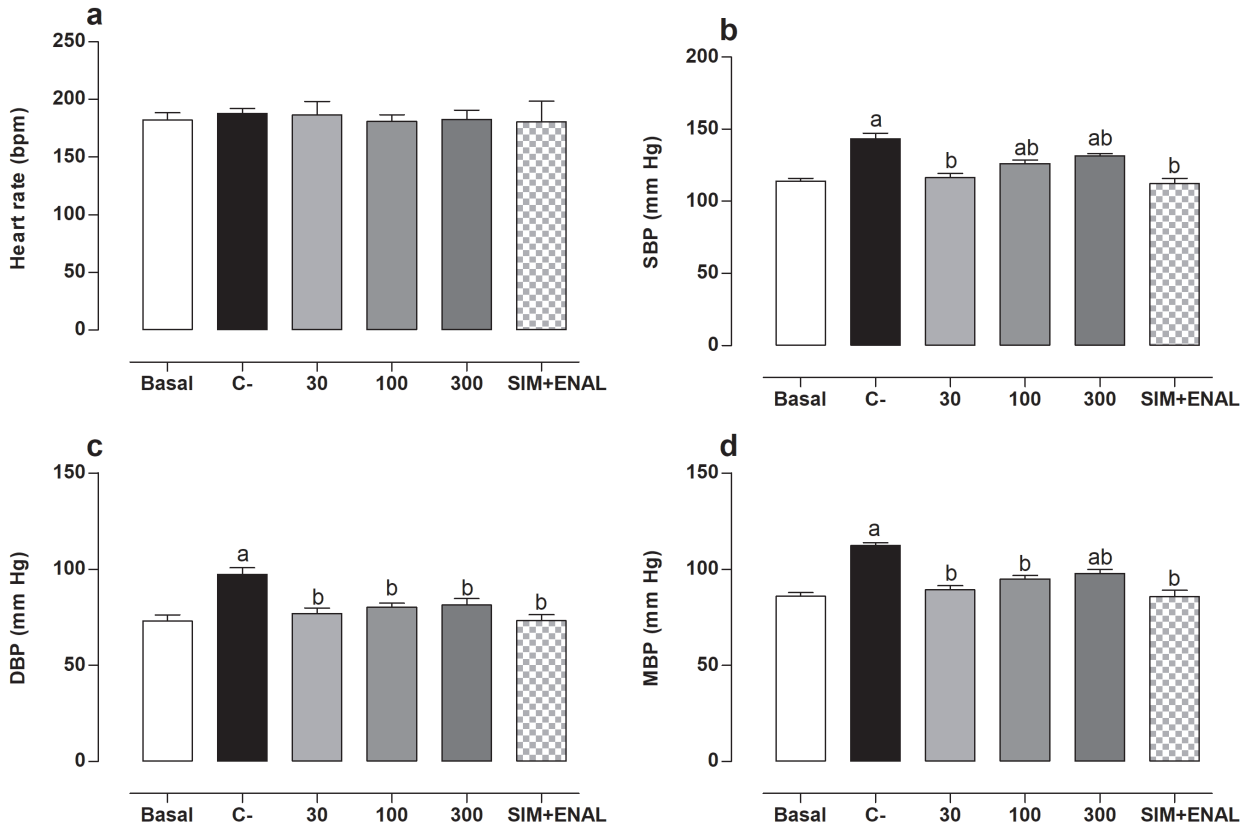

Figure 1. Heart rate (a), systolic blood pressure (b), diastolic blood pressure (c), and mean arterial pressure (d) in normotensive, non-dyslipidemic, and non-smoker Wistar rats (basal group) and hypertensive, dyslipidemic, and smoker Wistar rats that were treated with vehicle (negative control [C–]), *Baccharis trimera* (30, 100, and 300 mg/kg), and simvastatin + enalapril (SIM+ENAL). *n* = 8/group. The data are expressed as mean ± SEM. [a]*p* < 0.05, *vs.* basal; [b]*p* < 0.05, *vs.* C– (Kruskal-Wallis test followed by Dunn's *post hoc* test). bpm, beats per minute; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, median arterial pressure.

basal group (3.52 ± 0.03 mg/dL). Treatment with 30 mg/kg *B. trimera* completely reversed these alterations, whereas treatment with 100 and 300 mg/kg *B. trimera* and simvastatin + enalapril partially reversed these changes. No differences in globulin levels were found between groups (Table I).

Baccharis trimera exerts lipid-lowering effects

Hypertension, dyslipidemia, and smoking increased plasma triglyceride and cholesterol levels by 1030% and 206%, respectively, compared with the basal group (27.62 ± 0.98 and 37.59 ± 5.01 mg/dL, respectively; Fig. 3a, b). Treatment with 30 mg/kg *B. trimera* and simvastatin + enalapril completely reversed these increases in triglyceride and cholesterol levels, whereas 100 and 300 mg/kg *B. trimera* only partially reversed these changes (Fig. 3a, b).

Hypertension, dyslipidemia, and smoking increased hepatic triglyceride levels by 530% compared with basal values (24.02 ± 3.33 mg/dL). Treatment with all doses of *B. trimera* and simvastatin + enalapril partially reversed these changes in hepatic triglyceride levels (Fig. 3a). A 708% increase in hepatic cholesterol levels was observed in the C– group compared with the basal group (35.07 ± 9.11 mg/dL). Treatment with 30 mg/kg *B. trimera* completely reversed these increases in cholesterol levels. Treatment with

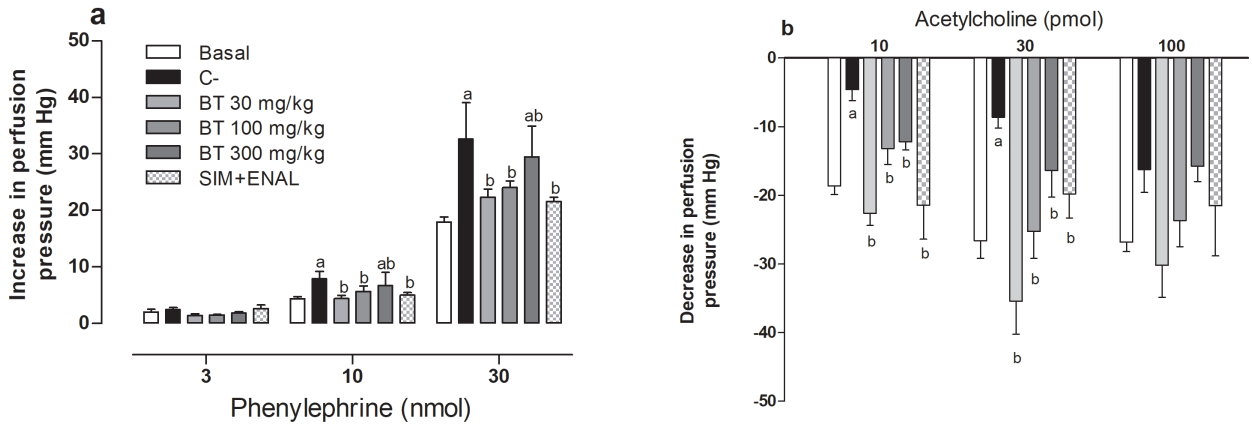

Figure 2. Perfusion pressure (mmHg) after an infusion of phenylephrine (a) and acetylcholine (b) in normotensive, non-dyslipidemic, and non-smoker Wistar rats (basal group) and hypertensive, dyslipidemic, and smoker Wistar rats that were treated with vehicle (negative control [C–]), *Baccharis trimera* (30, 100, and 300 mg/kg), and simvastatin + enalapril (SIM+ENAL). *n* = 8/group. The data are expressed as mean ± SEM. [a]*p* < 0.05, *vs.* basal; [b]*p* < 0.05, *vs.* C– (Kruskal-Wallis test followed by Dunn's *post hoc* test).

100 and 300 mg/kg *B. trimera* and simvastatin + enalapril partially reversed this increase (Fig. 3b). Finally, all doses of *B. trimera* increased the fecal excretion of triglycerides compared with the basal group (64.40 ± 4.77 mg/dL; Fig. 3a), but this increase was more evident for the 30 mg/kg dose of *B. trimera* (192% increase). The fecal excretion of cholesterol was increased by 30 and 100 mg/kg *B. trimera* compared with the C– group (116.70 ± 4.24 mg/dL; Fig. 3b).

Effects of *Baccharis trimera* on tecidual redox state

The combination of hypertension, dyslipidemia, and smoking induced cardiac, hepatic, and renal oxidative stress in rats (Table II). Decreases in cardiac, hepatic, and renal GSH levels (75.36 ± 4.84, 35.50 ± 2.95, and 60.47 ± 5.81 µg GSH/g tissue, respectively) were observed compared with the basal group (149.10 ± 15.89, 171.90 ± 5.60, and 122.60 ± 15.09 µg GSH/g tissue, respectively). Increases in cardiac, hepatic, and renal LPO levels were observed in the C– group compared with the basal group (82.96 ± 5.21, 69.95 ± 4.22, and 75.44 ± 5.21 mmol LPO/min/g tissue, respectively). These risk factors decreased cardiac SOD activity and increased hepatic and renal SOD activity compared with the basal group. Treatment with 30 and 100 mg/kg *B. trimera* completely reversed these changes, whereas 300 mg/kg *B. trimera* and simvastatin + enalapril partially reversed these changes.

Histological evaluation of the heart, liver, and kidneys and effects of *Baccharis trimera*

Histopathological alterations of the heart, liver, and kidneys are shown in Fig. 4. Myocardial lesions (Fig. 4a) in the basal group rats were classified as 0 (absence of lesions). In the C– group, moderate damage was observed (score 2; extensive myofibrillar degeneration and/or diffuse inflammatory process). Treatment with 30 mg/kg *B. trimera* reversed this myocardial damage (score 0). Treatment with 100 and 300 mg/kg *B. trimera* and simvastatin + enalapril exerted cardioprotective effects (score 1; focal myocyte damage or small multifocal degeneration with a slight degree of an inflammatory process). With regard to hepatic lesions (Fig. 4b), no alterations were observed in the basal group, and lesions in the C– group were classified as 3 (massive lesions). Treatment with 30 and 100 mg/kg *B.*

Table I. Plasma biochemical profile in hypertensive, dyslipidemic, and smoker Wistar rats that were treated with vehicle, *Baccharis trimera*, and simvastatin + enalapril.

			***Baccharis trimera* (mg/kg)**			
	Basal	**C–**	**30**	**100**	**300**	**SIM+ENAL**
AST (U/L)	33.90 ± 2.03	153.30 ± 5.65[a]	45.48 ± 0.80[b]	54.35 ± 0.55[a, b]	61.64 ± 1.33[a, b]	75.43 ± 1.63[a, b]
ALT (U/L)	27.75 ± 0.49	99.71 ± 4.84[a]	31.88 ± 0.53[b]	38.09 ± 0.61[a, b]	50.49 ± 2.39[a, b]	50.35 ± 0.96[a, b]
Urea (mg/dL)	28.74 ± 0.63	55.64 ± 3.64[a]	32.20 ± 0.26[b]	37.20 ± 1.15[a, b]	41.48 ± 0.37[a, b]	45.58 ± 0.81[a, b]
Creatinine (mg/dL)	0.35 ± 0.001	0.51 ± 0.006[a]	0.40 ± 0.008[b]	0.44 ± 0.007[a, b]	0.48 ± 0.01[a, b]	0.53 ± 0.03[a]
Albumin (g/dL)	3.52 ± 0.03	4.82 ± 0.16[a]	3.63 ± 0.02[b]	3.83 ± 0.02[a, b]	4.00 ± 0.03[a, b]	4.20 ± 0.06[a, b]
Globulin (g/dL)	2.06 ± 0.08	2.14 ± 0.07	2.34 ± 0.32	2.30 ± 0.15	2.42 ± 0.18	2.40 ± 0.04

C–, negative control; SIM+ENAL, simvastatin + enalapril. *n* = 8/group. The data are expressed as mean ± SEM. [a]*p* < 0.05, *vs.* basal; [b]*p* < 0.05, *vs.* C– (one-way ANOVA followed by Newman-Keuls *post hoc* test).

trimera exerted hepatoprotective effects (score 0.5; minor lesions). Treatment with 300 mg/kg *B. trimera* and simvastatin + enalapril exerted moderate hepatoprotective effects (score 2; marked lesions). With regard to renal alterations (Fig. 4c), the basal group had a damage score of 0% in all regions of the kidneys. Hypertension, dyslipidemia, and smoking induced moderate damage (26-50%) in all regions of the kidneys. Treatment with 30 and 100 mg/kg *B. trimera* exerted renoprotective effects in glomeruli (0% damage), tubules (1-25% damage), interstitium (0% damage), and vessels (0% damage). Treatment with 300 mg/kg *B. trimera* exerted moderate renoprotective effects in glomeruli (1-25% damage), tubules (1-25% damage), interstitium (1-25% damage), and vessels (0% damage). Treatment with simvastatin + enalapril also exerted moderate renoprotective effects in tubules (1-25% damage), interstitium (1-25% damage), and vessels (0% damage).

DISCUSSION

The present study investigated the hepatic and cardioprotective effects of *Baccharis trimera* using an experimental model that employed a combination of three important risk factors: hypertension, dyslipidemia, and tobacco smoking. Rats that were exposed to these risk factors exhibited expressive dyslipidemia and significant hepatic, renal, cardiac, and vascular changes. Daily treatment with an ethanol-soluble fraction of *B. trimera* for 4 weeks effectively reversed these changes, with effects that were similar or superior to the standard treatment (simvastatin + enalapril).

Previous studies showed that the *B. trimera* extract may exert several cardiovascular effects. Its secondary metabolites, including diterpenes, can block the contraction of vascular smooth muscles by extracellular calcium, inducing vasodilation and reducing blood pressure (Torres et al. 2000). Gómez et al. (2016) reported a vasorelaxant action of *B. trimera* extracts in aortic rings in Wistar rats. The present study also showed that the *B. trimera* extract reversed these

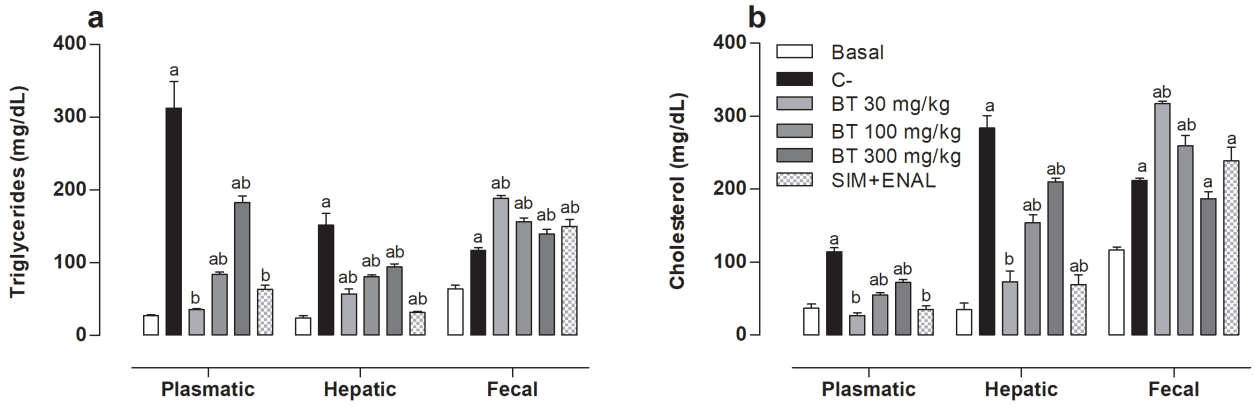

Figure 3. Plasma, hepatic, and fecal levels of (a) triglycerides and (b) cholesterol in normotensive, non-dyslipidemic, and non-smoker Wistar rats (basal group) and hypertensive, dyslipidemic, and smoker Wistar rats that were treated with vehicle (negative control [C–]), *Baccharis trimera* (30, 100, and 300 mg/kg), and simvastatin + enalapril (SIM+ENAL). *n* = 8/group. The data are expressed as mean ± SEM. [a]*p* < 0.05, *vs.* basal; [b]*p* < 0.05, *vs.* C– (one-way ANOVA followed by Newman-Keuls *post hoc* test).

changes that were induced by hypertension, dyslipidemia, and smoking in Wistar rats, thus demonstrating the cardioprotective effects of this medicinal species. These effects resulted from actions of metabolites that are present in *B. trimera*, especially polar phenolics as described previously (Souza et al. 2020).

Using an experimental model that associated diabetes, smoking, and dyslipidemia in Wistar rats, Souza et al. (2020) and Barbosa et al. (2020) reported plasma, hepatic, and fecal lipid-lowering effects of a *B. trimera* extract. Reductions of plasma, hepatic, and fecal levels of cholesterol and triglycerides were also found in mice in a model of alcoholic fatty liver disease (Lívero et al. 2016a). *B. trimera* exerts an inhibitory action on pancreatic lipase to prevent lipid hydrolysis and the absorption of triglycerides in the intestine. This effect also influences cholesterol levels, in which the availability of acetyl coenzyme-A that occurs through triglycerides induces the synthesis of cholesterol by the liver (Souza et al. 2020). In the present study, treatment with the *B. trimera* extract reestablished plasma levels of triglycerides and cholesterol. At the hepatic level, triglyceride levels were partially reversed in all of the treated groups, whereas hepatic cholesterol levels were completely recovered. Similarly, the fecal excretion of lipids was noticeably higher in the group that was treated with the *B. trimera* extract. This lipid-lowering effects of *Baccharis trimera* was compared to the simvastatin effects, which indicates that the extract of this medicinal plant can act in the reduction of lipids by mechanisms similar to that of statins, such as the inhibition of the enzyme 3-hidroxi-3-methyl-glutaril-CoA (HMG-CoA) reductase.

In addition to lipid-lowering effects, the hepatoprotective effects of *B. trimera* are also widely recognized. Its effect on the proliferation of hepatocytes was evident 24 h after partial hepatectomy in Wistar rats, demonstrating the impact of this plant on organ regeneration (Lima et al. 2017). Furthermore, using a model of paracetamol-induced hepatotoxicity, Pádua et al. (2014) reported a five-fold decrease in ALT and AST levels and histopathological changes in Fischer rats that were treated with a hydroethanolic extract of *B. trimera*. The hepatoprotective effect of *B. trimera* has also

Table II. Cardiac, hepatic, and renal markers of oxidative stress in hypertensive, dyslipidemic, and smoker Wistar rats that were treated with vehicle, *Baccharis trimera*, and simvastatin + enalapril.

			***Baccharis trimera* (mg/kg)**			
	Basal	**C–**	**30**	**100**	**300**	**SIM+ENAL**
Cardiac						
GSH	149.10 ± 15.89	75.36 ± 4.84[a]	216.00 ± 21.54[a, b]	157.80 ± 12.76[b]	139.70 ± 10.59[b]	87.03 ± 13.86[a]
LPO	82.96 ± 5.21	208.50 ± 12.54[a]	80.69 ± 6.42[b]	103.30 ± 4.97[b]	139.40 ± 15.77[a, b]	97.80 ± 4.74[b]
SOD	1654.0 ± 38.96	1371.0 ± 33.28[a]	1636.0 ± 59.01[b]	1481.0 ± 64.74[b]	1436.0 ± 37.07[a, b]	1444.0 ± 50.06[a, b]
Hepatic						
GSH	171.90 ± 5.67	35.50 ± 2.94[a]	183.10 ± 5.29[b]	149.10 ± 9.47[b]	141.50 ± 2.31[a, b]	127.70 ± 13.97[a, b]
LPO	69.95 ± 4.22	182.10 ± 4.61[a]	55.42 ± 3.40[b]	66.41 ± 1.26[b]	84.00 ± 1.84[b]	113.60 ± 10.26[a, b]
SOD	1190.0 ± 27.37	1508.0 ± 70.91[a]	1168.0 ± 23.50[b]	1298.0 ± 30.95[b]	1442.0 ± 34.53[a]	1565.0 ± 82.75[a]
Renal						
GSH	122.60 ± 15.09	60.47 ± 5.81[a]	135.30 ± 14.13[b]	109.80 ± 6.76[b]	73.62 ± 13.13[a]	113.10 ± 7.06[b]
LPO	75.44 ± 5.21	120.60 ± 12.62[a]	90.13 ± 3.02[b]	93.74 ± 2.87[b]	100.90 ± 2.73[b]	95.97 ± 1.51[b]
SOD	865.6 ± 21.42	964.8 ± 5.01[a]	937.2 ± 13.44[b]	995.0 ± 19.40[a]	985.5 ± 25.23[a]	953.3 ± 15.60[a]

C-, negative control; SIM+ENAL, simvastatin + enalapril; GSH, reduced glutathione (µg GSH/g tissue); LPO, lipoperoxidation (nmol LPO/min/mg tissue); SOD, superoxide dismutase (U SOD/mg of tissue). *n* = 8/group. The data are expressed as mean ± SEM. [a]*p* < 0.05, *vs.* basal; [b]*p* < 0.05, *vs.* C– (one-way ANOVA followed by Newman-Keuls *post hoc* test).

been described in a model of ethanol-induced hepatotoxicity. In Fischer rats that consumed absolute and diluted ethanol, a hydroethanolic extract of *B. trimera* reversed hepatic steatosis (Rabelo et al. 2018). In a model of alcoholic hepatic steatosis, Lívero et al. (2016a) reported the normalization of AST and ALT levels and anti-steatosis effects in Swiss mice that were treated with a hydroethanolic extract of *B. trimera*. The present study used a model that employed a combination of three different risk factors for chronic noncommunicable diseases and found hepatoprotective effects of the *B. trimera* extract, indicating that the therapeutic effects of this extract may be useful for liver diseases that are attributable to different causes.

Another important effect observed in this study was the antioxidant activity of *B. trimera*. As lipids are susceptible to oxidation, lipid peroxidation products are important biomarkers of oxidative stress *in vivo* and diseases related to this process and its prevention can maintain homeostasis (Etsuo 2008). The GSH (one of the most powerful intracellular antioxidants) together with the potential cellular redox are components of the cell signaling system that influence the translocation of the NF kappa B transcription factor, an element that regulates the synthesis of adhesion molecules and

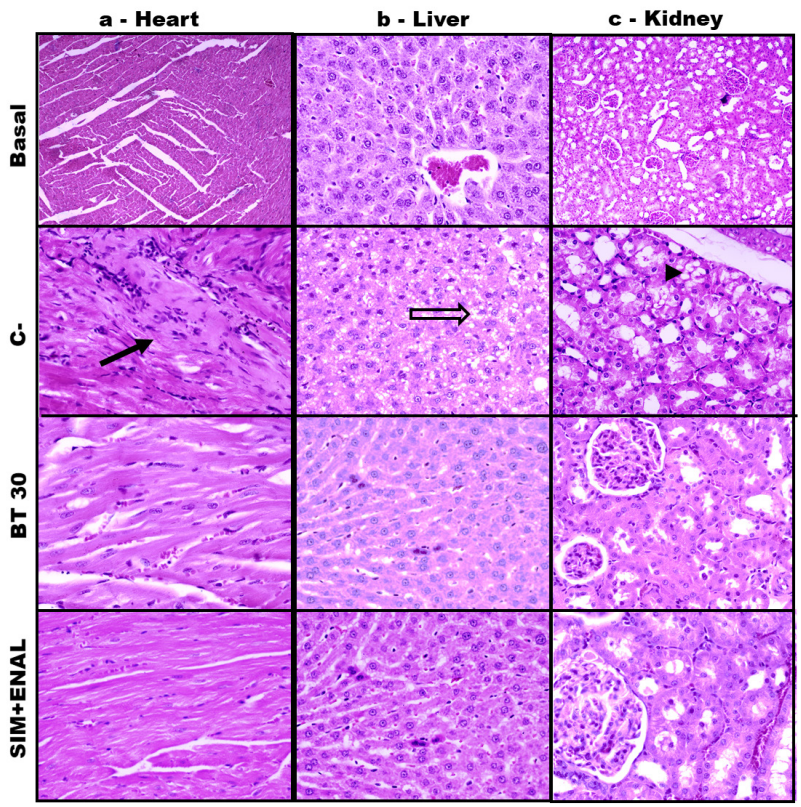

Figure 4. Histopathological evaluation of the heart (a), liver (b), and kidneys (c) in normotensive, non-dyslipidemic, and non-smoker Wistar rats (basal group) and hypertensive, dyslipidemic, and smoker Wistar rats that were treated with vehicle (negative control [C–]), 30 mg/kg *Baccharis trimera* (BT 30), and simvastatin + enalapril (SIM+ENAL). The *black arrow* indicates fibrosis. The *open arrow* indicates steatosis. The *black arrowhead* indicates tubular degeneration.

cytokines. In this way, the restoration of GSH levels protects the cell against oxidative damage (Exner et al. 2000). Added to the role of GSH is the antioxidant action of SOD, since impairment in SOD activity can compromise cell function from defects in amino acid metabolism to increased oxidative damage to DNA (Culotta 2001).

B. trimera modulates tecidual antioxidant defense system against free radicals and reactive oxygen species, which may cause cell damage through the oxidation of components of cytoplasmic membranes, reaching the nucleus and triggering damage to cellular DNA. However, the antioxidant activity of *B. trimera* may vary by the type of preparation of the extract. The specific solvent that is used can alter levels of different plant metabolites, such as flavonoids and phenolic compounds. Extracts of *B. trimera* that were prepared with polar solvents had the greatest antioxidant effects because phenolic compounds are extracted more easily in these preparations (Simões-Pires 2005, Oliveira et al. 2012, Rabelo & Costa 2018). The antioxidant activity of an aqueous extract of *B. trimera* was observed in Wistar rats that exhibited hepatic lipid peroxidation using iron and sodium nitroprusside. A *B. trimera* extract reduced lipid peroxidation, increased catalase activity, and increased hepatic glutathione levels (Sabir et al. 2017). Increases in catalase activity and decreases in glutathione levels were also observed in Fischer rats that were subjected to acetaminophen-induced hepatotoxicity (Pádua et al. 2014). Swiss mice that were treated with a hydroethanolic extract of *B. trimera* and were subjected to a model of alcoholic fatty liver exhibited positive modulation of the entire liver antioxidant system (Lívero et al. 2016a). Similar findings were described in two other studies that used a preclinical model that associated diabetes, dyslipidemia, and smoking in Wistar rats (Barbosa et al. 2020, Souza et al. 2020). In

the model that employed a combination of dyslipidemia, hypertension, and smoking in the present study, cardiac, hepatic, and renal oxidative stress significantly increased, which was normalized by treatment with the *B. trimera* extract. Thus, reestablishment of the antioxidant defense system may have contributed to minimizing cellular damage and attenuating changes in vascular reactivity and histological lesions in the heart, liver, and kidneys.

One limitation of the present study was that we did not evaluate the molecular mechanisms that underlie the hepatic and cardioprotective effects of *B. trimera*. The hepatic and cardioprotective effects of *B. trimera* were very similar to the effects of two classic cardioprotective drugs, enalapril and simvastatin. Contrary to expectations that a classic dose-response effect would be observed, we found a better pharmacological response to the lowest dose of *B. trimera* (30 mg/kg). This relatively low dose exerted important hepatic and cardioprotective effects; in some instances, this dose exerted better effects than the classic enalapril + simvastatin combination. Such a response pattern is common with the use of crude plant extracts. The concentrations of various secondary metabolites can vary by extract dose. The concentrations of constituents of *B. trimera* that are responsible for its therapeutic activity are greater when the lowest dose of the extract is used. The concentrations of molecules that antagonize the beneficial effects of active constituents may increase at higher doses of the extract.

B. trimera is already incorporated in most official pharmacopeias and has been shown to be devoid of toxicity in humans based on historical use. Overall, our findings suggest that *B. trimera* may be safe and useful for treating patients with cardiovascular and hepatic disorders, especially disorders that are associated with multiple risk factors, such as hypertension, smoking, and dyslipidemia.

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TCM, GRS, AOS, MIS, LPG, RACP, CTS, JDDB, PAA, ECA and FARL were responsible for the experiments and data analyzed. DLF contributed to the histological analyses. AAS and GRS contributed to the extract preparation. TCM, AGJ and FARL were responsible for data discussion and manuscript elaboration. TCM, ECWL, JTRP, and AGJ contributed to data interpretation and manuscript preparation and made critical revisions of the manuscript for intellectual content. FARL conceived the project, designed the experiments, obtained financial support and was the senior researcher who was responsible for the project. The authors declare that they have no conflict of interest.