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Polyphenol-rich extract of *Syzygium cumini* (L.) Skeels leaves improves the metabolic profile and redox status of dexamethasone-induced diabetic rats

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ABSTRACT

Diabetes is an endemic disease that affects a large portion of the global population. As a result, the search for new antidiabetic drugs and supportive treatments is crucial to combat this widespread condition. *Syzygium cumini* (L.) Skeels (Myrtaceae), popularly known as "jambolão," reportedly has antioxidant, anti-inflammatory, and antidiabetic properties. This study aimed to evaluate the effects of the polyphenol-rich extract of *Syzygium cumini* leaves (PESc) on the metabolic profile and redox status of dexamethasone-induced diabetic rats. Male Wistar rats were randomly assigned to three groups: control group (CTRL), rats that received 0.9% saline solution (1 mL/kg/day, v.o., 10 days); dexamethasone group (DEX), rats that received dexamethasone (1 mg/kg/day, i.p., 5 days); and experimental group (PESc+DEX), rats that were pre-treated with PESc (500 mg/kg/day, v.o.), for 5 days prior to and during the dexamethasone regime. Fasting blood glucose and serum triglycerides increased in the DEX group compared to CTRL, which were reduced by the treatment with PESc. Similar effects were observed with serum insulin. We also observed that under hyperglycemic conditions, PESc-treated animals reversed the dexamethasone-induced insulin hypersecretion. However, the redox status was mildly affected by PESc treatment. Both superoxide dismutase and catalase activity increased in DEX group in comparison to CTRL, however PESc treatment attenuated only catalase activity. Moreover, serum hydroperoxides also increased in DEX, but was attenuated with PESc treatment. Our findings support the antidiabetic effects of PESc with a direct modulation on the insulin secretion, which appears to be partially related to redox-dependent mechanisms.

1. Introduction

Type 2 diabetes mellitus (T2DM) is a significant public health issue, with widespread impact on quality of life and healthcare costs. The global prevalence of T2DM has risen sharply, largely due to rapid economic development and urbanization. This disease impairs individuals' functional capacities and quality of life, leading to high morbidity and premature mortality rates [1]. T2DM is a complex metabolic disorder characterized initially by hyperinsulinemia and increased insulin resistance in peripheral tissues. As it progresses, β-cell function deteriorates, resulting in reduced insulin biosynthesis and secretion. This decline disrupts the metabolism of carbohydrates, proteins, and lipids [2]. One of the important issues of T2DM pathology is oxidative stress. Metabolic disturbances in T2DM activate NADPH oxidases (NOXs) and increase the production of reactive oxygen species (ROS) from mitochondria and other cellular sources, particularly in the pancreas [3]. β-cells, which are located in the pancreas and synthesize insulin, are especially vulnerable to oxidative damage not only because β-cells are

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continually exposed to excessive ROS during metabolic disturbances [4, 5], but also due to their limited antioxidant defenses. β-cells lack catalase and have low levels of glutathione peroxidase, making them less capable of managing oxidative stress [6]. In addition, increased oxidative stress also inactivates critical β-cell transcription factors, such as pancreatic and duodenal homeobox 1 (PDX1) and MafA. This inactivation reduces proinsulin synthesis and disrupts the expression of genes essential for β-cell differentiation, proliferation, and survival, further compromising insulin production [7].

Plant-derived compounds have been utilized in traditional medicine worldwide since ancient times [8]. Polyphenols are one of the most important groups of plant secondary metabolites. They have garnered global attention as nutraceuticals for preventing various diseases, including T2DM, as are excellent antioxidants [9]. In this context, *Syzygium cumini* (L.) Skeels, also known by its synonym *Eugenia jambolana* and commonly referred to as "jambolão," is a medicinal plant of Indian origin belonging to the Myrtaceae family [10]. Various parts of the plant, including leaves, bark, roots, fruits, flowers, and seeds are prepared and used based on their therapeutic properties, such as antihyperglycemic, antidiarrheal, antimicrobial, antioxidant, hypolipidemic, cardioprotective, and hepatoprotective activities [11]. The fruits of *S. cumini* are well known for their high concentration of phenolic compounds, including monomeric anthocyanins, gallic acid, and derivatives of quercetin and myricetin [12–14]. Additionally, the hydroalcoholic extract from the leaves of this plant is rich in flavonoids such as myricetin, and its derivatives [15,16].

Experimental and clinical studies have identified *S. cumini* as a promising therapeutic agent, with different plant parts used to manage diabetes [17]. The antidiabetic properties observed in the bark act through both pancreatic and extra-pancreatic mechanisms [10]. Moreover, the seeds exhibit a protective effect on β-cells, preventing necrosis induced by alloxan [18]. In addition, the oral administration of the hydroethanolic extract of *S. cumini* leaves has demonstrated hypoglycemic effects and potential protective action against oxidative stress and DNA damage in diabetic animals induced with a high-fat diet and streptozotocin (HFD+STZ) [19]. Using the same animal model, Sharma et al. (2012) have shown that the treatment with aqueous extract from seeds significantly prevented hyperglycemia, hyperinsulinemia, and elevated expression of pancreatic antioxidant enzymes. Furthermore, the pathological changes in islets and β-cells caused by HFD+STZ were reversed to near-normal levels following treatment with *S. cumini*, which also increased protein expression of PPARγ and PPARα in the liver [20].

Previously, we have demonstrated that the polyphenol-rich extract from *S. cumini* leaves (PESc) modulates insulin secretion by INS-1E β-cells [16]. Therefore, in this study, we employed an in vivo model of dexamethasone-induced diabetes to further investigate the effects of PESc on the metabolic profile and redox status of diabetic rats. Our results demonstrated that PESc treatment enhanced insulin secretion and improved certain metabolic parameters. Overall, these findings suggest that under our experimental conditions, PESc exhibits antidiabetic potential which appears to be partially related to redox-dependent mechanisms.

2. Materials and methods

2.1. Plant collection, identification, and preparation of polyphenol-rich extract

Leaves of the *S. cumini* plant species were collected on the campus of the Federal University of Maranhão (UFMA, São Luís–MA, Brazil; 2,5555° S, 44,3098° W; WGS84). An exsiccated sample of the plant species was identified and stored at the Herbarium of Maranhão (MAR) under the register number 4574. The PESc was prepared as previously described and submitted to HPLC-MS/MS for confirmation of the described phytochemical profile [16]

2.2. Animals and experimental groups

Males Wistar rats (*Rattus norvegicus*, 90 days old) were obtained from the Central Animal Facility at UFMA. The animals were housed in polyethylene cages lined with wood shavings, kept in a controlled environment (22 ± 2 °C) with a 12-hour light/dark cycle, and provided with free access to water and standard chow. All experimental protocols were approved by the Animal Use Ethics Committee – CEUA/UFMA. After a week of acclimation to these conditions, the rats were randomly assigned to three groups, consisting of at least 8 animals each. As displayed in Fig. 1, the experiment lasted a total of 11 days, with the groups defined as follows: **1.** Control Group (CTRL): Rats received daily oral treatment via gavage with 0.9% saline solution (1 mL/kg/day) for 10 days. **2.** Dexamethasone only Group (DEX): Rats were treated daily via gavage with 0.9% saline solution (as in 1), and on day 6 and beyond, the animals also received dexamethasone (1 mg/kg/day, i.p.) as previously described [21]. **3.** PESc + DEX Group: Rats were treated daily with 500 mg/kg of PESc via gavage throughout the experimental period, followed by diabetes induction with DEX (1 mg/kg/day, i.p.) from day 6–10. Group **1** also received i.p. saline injections from day 6–10. The body weight was recorded daily over the entire period. On day 11, rats were euthanized under anesthesia (10 mg/kg xylazine, 40 mg/kg ketamine) after 12-h fasting to blood sample collection by abdominal aorta puncture. Liver, pancreas, gastrocnemius, and soleus skeletal muscle, as well as retroperitoneal, and periepididymal fat pads were collected for morphometric assessment, which were expressed as the tissue mass (g) per 100 g body weight (% BW).

2.3. Serum biochemical analysis

The biochemical parameters were monitored in the blood at the end of the treatment after a 12-hour fasting period. Blood samples were centrifuged at 3500 rpm for 5 min to separate serum. Glucose, total cholesterol, triacylglycerides, levels were assessed in serum samples using spectrophotometric commercial kits according to the manufacturers' instructions (Labtest, MG, Brazil).

2.4. Serum insulin

To assess insulin levels in the serum, radioimmunoassay was utilized. Briefly, 0.1 mL of serum was mixed with 0.2 mL of an anti-insulin antibody solution (1:300,000) and insulin ^{125}I-labeled insulin, in phosphate buffer (pH 7.4) containing 0.9% NaCl and 0.5% albumin. The mixture was vortexed and incubated at 4 °C, for 48 h. After, 0.2 mL of adsorbing solution (2.5% charcoal (Norit A), 0.5% albumin, and 0.25% dextran T-70) was added to each tube. Tubes were left undisturbed for 20 min and then centrifuged (20 min, 2800 rpm, 4°C). The supernatant was discarded, and radioactivity in each tube was measured using a gamma radiation counter. Insulin concentrations (ng/mL) in the samples were determined using the standard curve [22].

2.5. Evaluation of insulin secretion in isolated islets

To evaluate the secretion of insulin in the different groups, we evaluated the secretion of insulin using isolated islets from animals after euthanasia. First, the pancreatic duct was infused with 0.8 mg/mL of collagenase type V in Hanks' buffer containing 5.6 mM of glucose and 0.05% of bovine serum albumin fraction V (BSA); Sigma-Aldrich, USA). After isolation, the tissue was incubated in a water bath at 37°C for 25 min and subsequently, the material was washed four times with Hanks' solution containing 0.3% BSA and 5.6 mM of glucose. The collected islets (5 sets of 4 islets per group) were pre-incubated in Krebs-Henseleit buffer with HEPES (KRBH), pH 7.4, supplemented with 0.3% BSA and 5.6 mM glucose for 45 min at 37°C in a controlled environment (gassed with 95% O_2 and 5% CO_2). After pre-incubation, the medium was discarded, the islets were with low (5.6 mM) or high (16.7 mM)

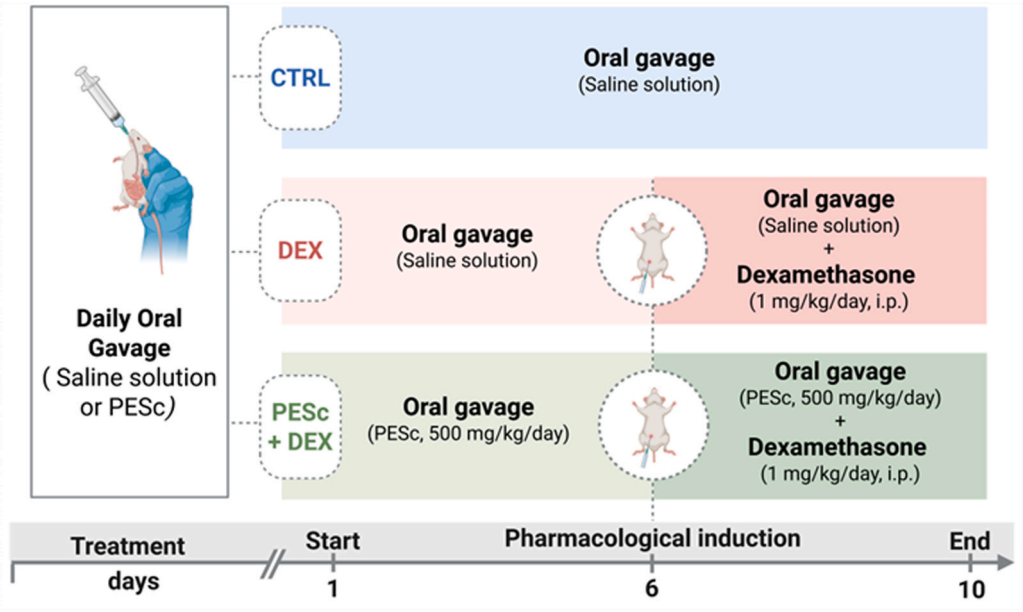

Fig. 1. Flowchart of the dexamethasone-induced T2DM protocol and treatment with the polyphenol-rich extract of *Syzygium cumini* (PESc).

concentration of glucose, respectively. The insulin secretion was measured by radioimmunoassay as described in 2.4.

2.6. Insulin resistance

Insulin resistance was assessed by two well-known methods, the TyG index (TyG = natural logarithm fasting TAG mg/dL × fasting GL mg/dL /2) [23], and the homeostasis model assessment of insulin resistance (HOMA-IR = 636 × fasting insulin (U/mL)/fasting glucose (mM) / 22.5). Additionally, the homeostasis model assessment of β-cell function (HOMA-%B = 20 × fasting insulin (U/mL) / fasting glucose (mM) - 3.5) was calculated as a surrogate for β-cell secretory capacity [24].

2.7. Assessment of triacylglycerol and cholesterol levels in the liver

Fat liver was assessed according to modifications of the method described in Freedman [25]. Fat extraction was performed by homogenizing 500 mg of tissue with 5 mL of a chloroform/methanol mixture (2:1) and incubating the mixture overnight at 4–8°C. The tissue was then separated by filtration, and 0.9% NaCl solution (1 part saline: 5 parts filtrate) was added to the filtrate. This mixture was vortexed, allowed to rest for 2 h, and then centrifuged to separate the methanolic and chloroform phases. A specific volume of the organic phase was collected and dried, leaving only the solid fat mass, which was weighed. Finally, the fat was resuspended in Triton X-100/methanol (2:1) for the determination of triacylglycerol and cholesterol concentrations using colorimetric enzymatic assays according to manufacturer's instructions as in 2.3.

2.8. Systemic redox status

The activities of catalase (CAT), superoxide dismutase (SOD) and glutathione peroxidase (GPx) in serum from anticoagulant-free blood collected from abdominal aorta were performed following manufacturer's instructions (Cayman Chemical®). The total hydroperoxide (LOOH) was measured according to the method described by Jiang et al. [26], using a H_2O_2 (0.025–0.4 mM) standard curve, and the results expressed as mg LOOH per mg protein. Serum malondialdehyde (MDA) levels were measured using the TBARS assay, as previously described [27]. Serum samples were reacted with trichloroacetic acid and thiobarbituric acid, heated in a boiling water bath, and the resulting chromogen was extracted with butanol and measured spectrophotometrically at 535 nm. Results were calculated using 1,1,3,3-tetramethoxypropane as standard and expressed as μM MDA.

2.9. Statistical analysis

The results were expressed as the mean ± standard error of the mean (S.E.M.). Data analysis was performed using parametric statistical tests (ANOVA followed by the Newman-Keuls post hoc test) or non-parametric tests (ANOVA followed by the Kruskal-Wallis or Dunn's post hoc test) and analyzed using GraphPad Prism® software (version 10.0). A significance level of $p \leq 0.05$ was considered statistically significant.

3. Results

3.1. Effects of PESc on weight gain and morphometric parameters

Routine weight monitoring revealed differences in weight progression between the CTRL and PESc groups as early as day 6, when diabetes induction with dexamethasone (DEX) began. Notably, PESc treatment

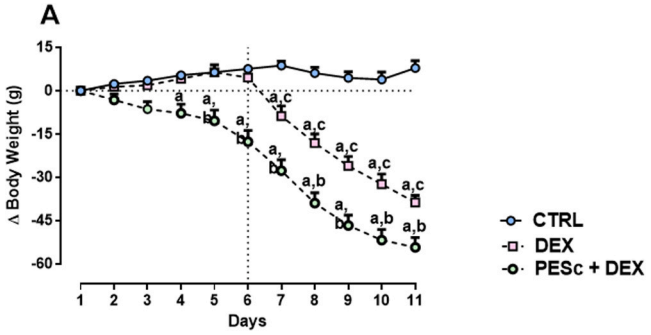

Fig. 2. Effects of the hydroethanolic extract from *Syzygium cumini* leaves on the body weight of male Wistar rats. Data are presented as mean ± SEM and statistical differences were evaluated using two-way ANOVA, followed by the Newman–Keuls post hoc test (GraphPad Prism®), with a significance level of $p < 0.05$. (a) Difference compared to the CTRL group (b) difference compared to the DEX group (c) difference compared to the PESc + DEX group.

induced weight loss by day 3, leading to a total decrease of 17.66 ± 3.66 g ($p < 0.05$) by day 6 (Fig. 2), when compared to the CTRL group (Fig. 2). In the DEX group, a marked weight loss was observed as early as the first day of diabetes induction (day 7) and continued thereafter when compared to the CTRL group, reflecting a classical outcome from dexamethasone-induced T2DM in rodents. Furthermore, the PESc + DEX group exhibited sustained significant weight loss compared to the CTRL, and in a similar rate to DEX groups. These findings demonstrate that PESc treatment decreases body weight and does not interfere with weight loss caused by DEX.

Next, we investigated the effects of PESc on the morphometric parameters of liver, skeletal muscles (gastrocnemius and soleus), and adipose tissues, specifically the retroperitoneal and periepididymal fat pads (Table 1). We observed that the only parameter that was affected was the retroperitoneal fat pad, which was diminished in both DEX and PESc + DEX. This result suggested that pre-treatment with PESc does not affect the classical deleterious effects of DEX on adipose tissue.

3.2. Effect of PESc on glucolipid metabolism

As expected, the induction of T2DM with dexamethasone increased fasting blood glucose levels in the DEX group by 34.1% (125.6 ± 3.20 mg/dL) compared to the CTRL group (93.6 ± 1.97 mg/dL). Treatment with PESc mitigated the hyperglycemic effect of DEX since fasting blood glucose levels in this group were reduced by about 9% when compared to DEX group (Fig. 3A). No statistically significant differences were observed between groups in total serum cholesterol levels (Fig. 3B). However, serum triacylgycerol levels increased by 142.5% in the DEX group (196.5 ± 14.7 mg/dL) compared to the CTRL group (81.02 ± 10.5 mg/dL), and again PESc attenuated this effect (Fig. 3C). Finally, serum insulin levels in the DEX group (5.79 ± 1.18 ng/mL) were approximately 10 times higher than those in the CTRL group and pre-treatment with PESc reduced insulin levels in the DEX + PESc group to 2.31 ± 1.07 ng/mL, which was four times higher than the CTRL group but not statistically different (Fig. 4D). These findings indicated that PESc pre-treatment attenuated some of the metabolic disturbances caused by DEX.

Regarding glucolipid metabolism in the liver, dexamethasone alone, as well as treatment with PESc + DEX, did not alter the total hepatic fat content or the hepatic cholesterol fraction (Figs. 4A and 4C, respectively). However, dexamethasone alone caused a robust increase in hepatic TAG content when compared to the CTRL group, and the pre-treatment with PESc completely prevented this triacylglycerol accumulation in diabetic rats (Fig. 4B).

3.3. Effect of PESc on peripheral insulin resistance and secretory activity of the endocrine pancreas

The assessment of peripheral insulin sensitivity, determined through the calculation of the TyG and HOMA-IR indices, showed that dexamethasone administration in reduced insulin sensitivity compared to the CTRL group. The pre-treatment with PESc attenuated this effect by improving insulin sensitivity, as observed in both tests (Figs. 5A and 5B). The HOMA-%B index was calculated to evaluate β-cell secretory activity in the experimental groups. The DEX group presented a significantly higher index than the CTRL animals. Although not significantly statistically PESC pre-treatment mitigated this augmentation, as observed in the PESc + DEX group (Fig. 5C).

To assess β-cell secretory activity, insulin secretion was stimulated by glucose in isolated pancreatic islets from CTRL, DEX, and PESc + DEX rats. The data shown in Fig. 7 indicates that under basal conditions (glucose 5.6 mM), islets from DEX and PESc + DEX animals exhibited increased basal insulin secretion compared to islets from CTRL animals. When glucose concentration increased to 16.7 mM, islets from CTRL animals responded with the expected increase in insulin secretion. Furthermore, islets from DEX animals showed an even greater response compared to the CTRL group and pre-treatment with EHSc (PESc + DEX group) the hypersecretion induced by dexamethasone was abolished, returning to CTR levels (Fig. 6).

Table 1
Morphometric parameters of control and diabetic rats treated with PESc.

Morphometric parameters	CTRL	DEX	PESc + DEX
Liver (%BW)	3.40 ± 0.1	3.44 ± 0.1	3.46 ± 0.06
Periepididymal fat (%BW)	0.863 ± 0.02	0.780 ± 0.05	0.915 ± 0.08
Retroperitoneal fat (%BW)	0.659 ± 0.01	0.387 ± 0.02*	0.433 ± 0.03*
Skeletal muscles (%BW)	0.762 ± 0.02	0.619 ± 0.04	0.610 ± 0.03

Values are expressed as mean ± SEM * Indicates a statistically significant difference compared to the CTRL group, as analyzed by ANOVA followed by the Kruskal-Wallis post hoc test (GraphPad Prism®), *$p < 0.05$.

3.4. Effect of PESc on the antioxidant enzymes and oxidative parameters

To evaluate the redox status of diabetic rats and whether pre-treated with PESc would affect it, we assessed the activity of key antioxidant defense enzymes, including superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx), in the serum of animals from different groups. SOD activity was significantly higher in the DEX group compared to the CTRL group, and pre-treatment with PESc did not alter this outcome (Fig. 7A). Similarly, CAT activity was elevated in the DEX group; however, pre-treatment with PESc partially prevented these animals from reaching the highest activity levels observed in the DEX group (Fig. 7B). No significant changes in GPx activity were observed under any experimental condition (Fig. 7C). To further evaluate potential oxidative damage caused by DEX treatment, we quantified hydroperoxide levels as well MDA as a marker of lipid peroxidation. Hydroperoxide levels in the DEX group were 27.2% higher than in the CTRL group, but this increase was attenuated in the PESc+DEX group (Fig. 7D). Similar increase in MDA was observed in the DEX group; however, PESc treatment significantly reduced MDA levels back to control values (Fig. 7E). These findings suggest that dexamethasone-induced type 2 diabetes (DM2) is associated with an increased oxidative profile, and PESc may attenuate this pro-oxidative scenario in diabetic rats.

4. Discussion

In this study, we utilized a rodent model of dexamethasone-induced diabetes to cause insulin resistance and metabolic alterations similar to those observed in T2DM [21,28,29]. Our findings demonstrate the antidiabetic potential of PESc, as treatment with this extract significantly reduced fasting serum glucose, triacylglycerol, and insulin in PESc +DEX rats. Furthermore, the treatment reversed hepatic triacylglycerol accumulation, enhanced peripheral insulin sensitivity, and reduced hyperglycemia-induced insulin hypersecretion in isolated pancreatic islets from PESc-treated animals. These beneficial effects appear to be associated with improvements in the systemic redox balance, as indicated by reduced serum lipid peroxidation and decreased catalase activity, suggesting attenuation of dexamethasone-induced oxidative stress.

An important aspect related to the potential antidiabetic effects of PESc is its impact on body weight. Pre-treatment with PESc led to a reduction in body weight even before dexamethasone administration. The weight-reducing effect of PESc is consistent with previous studies, which have shown that extracts prepared from different parts of *S. cumini* can promote weight loss in rats [15,30]. However, PESc did not further potentiate dexamethasone-induced weight loss, as the slopes of both curves were similar. This suggests that high circulating glucocorticoid levels masks the effect of PESc on body weight. While long-term dexamethasone use in humans is typically associated with weight gain [31,32], in rodents, it can result in weight loss, likely due to increased

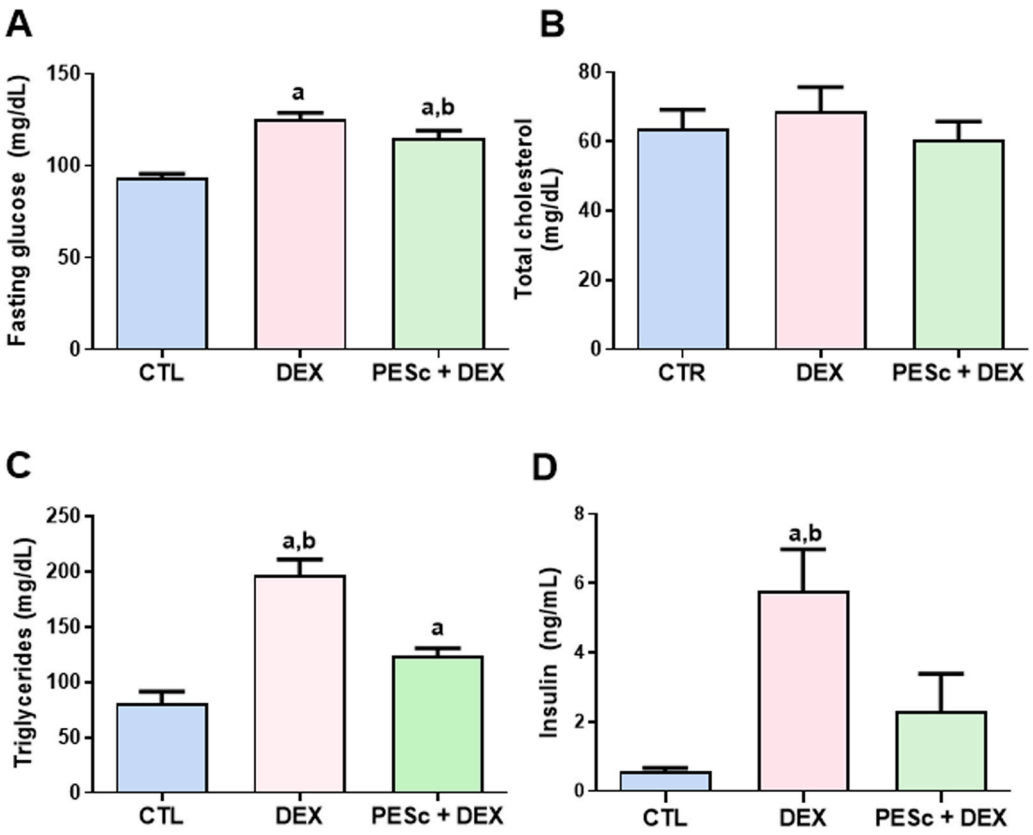

Fig. 3. Effects of the PESc on biochemical parameters in the serum. (A) fasting glucose (B) total cholesterol (C) TAG and (D) insulin. Data are presented as mean ± SEM and statistical differences were evaluated using two-way ANOVA, followed by the Newman–Keuls post hoc test (GraphPad Prism®), with a significance level of $p < 0.05$. (a) Difference compared to the CTRL group; (b) difference compared to the DEX group.

overall catabolic activity [33] and hypothalamic suppression of food intake induced by hyperinsulinemia [21,34–36]. Another important observation is that dexamethasone administration alone resulted in a significant reduction in the relative weight of retroperitoneal fat only. This effect may be linked to increased lipolytic activity in non-visceral white adipose tissue, stimulated by glucocorticoids [37]. Corroborating this observation, Rafacho and co-workers [21] evaluated fat pads in animals treated with varying doses of dexamethasone (0.1–1 mg/kg/day) and similarly reported a reduction exclusively in retroperitoneal fat. However, this finding contrasts with other studies indicating that dexamethasone treatment (1 mg/kg/day) in rats resulted in increased periepididymal fat, with variable effects on other fat pads [28,34,38].

Despite those discrepancies regarding white adipose tissue responses, our data confirm that dexamethasone induced increases in fasting triglycerides and glycemia, as expected [36] and the PESc pre-treatment attenuated these negative effects. It is well established that the negative effects of glucocorticoids on glycemic homeostasis are dependent on dose and/or duration of exposure, leading to elevated plasma triglycerides and insulin levels, as well as hepatic lipid accumulation, which may or may not be accompanied by fasting hyperglycemia [21,29,34,36,39]. In our study, PESc pre-treatment significantly reduced hepatic triglyceride content, bringing it to levels comparable to the control group. Similarly, in a metabolic syndrome rat model induced by monosodium glutamate, PESc was also shown to reduce both serum and hepatic triglyceride levels [15]. By lowering hepatic triglycerides, PESc pre-treatment reduced the TyG index, a parameter strongly correlated with early indicators of insulin resistance [40]. In addition, PESc also improved serum insulin levels, serum lipid profile, and visceral adipose tissue accumulation [15].

Several experimental studies have demonstrated that glucocorticoids reduce insulin sensitivity in rats while simultaneously stimulating insulin secretion [36,39,41]. In our DEX-induced T2DM model, a reduction in insulin sensitivity was observed, and PESc pre-treatment restored peripheral insulin sensitivity, as indicated by the HOMA-IR index, while also improving β-cell secretory function. Furthermore, consistent with the *ex vivo* β-cell secretory activity data, DEX-treated animals exhibited insulin hypersecretion under both basal (5.6 mM) and hyperglycemic conditions (16.7 mM glucose). Nevertheless, PESc pre-treatment prevented insulin hypersecretion under hyperglycemic conditions.

Our data indicate that PESc improves metabolic parameters associated with dexamethasone-induced T2DM. These effects may be attributed to the bioactive compounds that we have identified in the leaves [16] and other parts of *S. cumini*, as reported in studies of other plant extracts, which are known to directly influence insulin biosynthesis, secretion, and action, as well as improve metabolic parameters [17,42,43]. Moreover, oral administration of ethyl acetate fractions of *S. cumini*, which are similar to PESc, have shown to restore hepatic hexokinase and glucose-6-phosphatase activity, leading to improved serum glucose levels, lipid profiles, and glycogen content in the liver and muscles of diabetic rats. In addition, studies have demonstrated that *S. cumini* and its isolated compounds activate L-type calcium channels, which play a crucial role in insulin secretion [44,45].

In animal models of T2DM associated with oxidative stress, such as dexamethasone-induced diabetes [46], improvements in metabolic profiles and insulin sensitivity may also be linked to the antioxidant properties of compounds in the plant extract [47,48]. Our research group has characterized the key phytochemicals in PESc, including flavonoids derived from myricetin as the predominant components [15,16]. Myricetin and its derivatives are known for their potent antioxidant activity [49], their ability to enhance insulin signaling in skeletal muscle [50] and adipocytes [51], and their protective effects on β-cells against

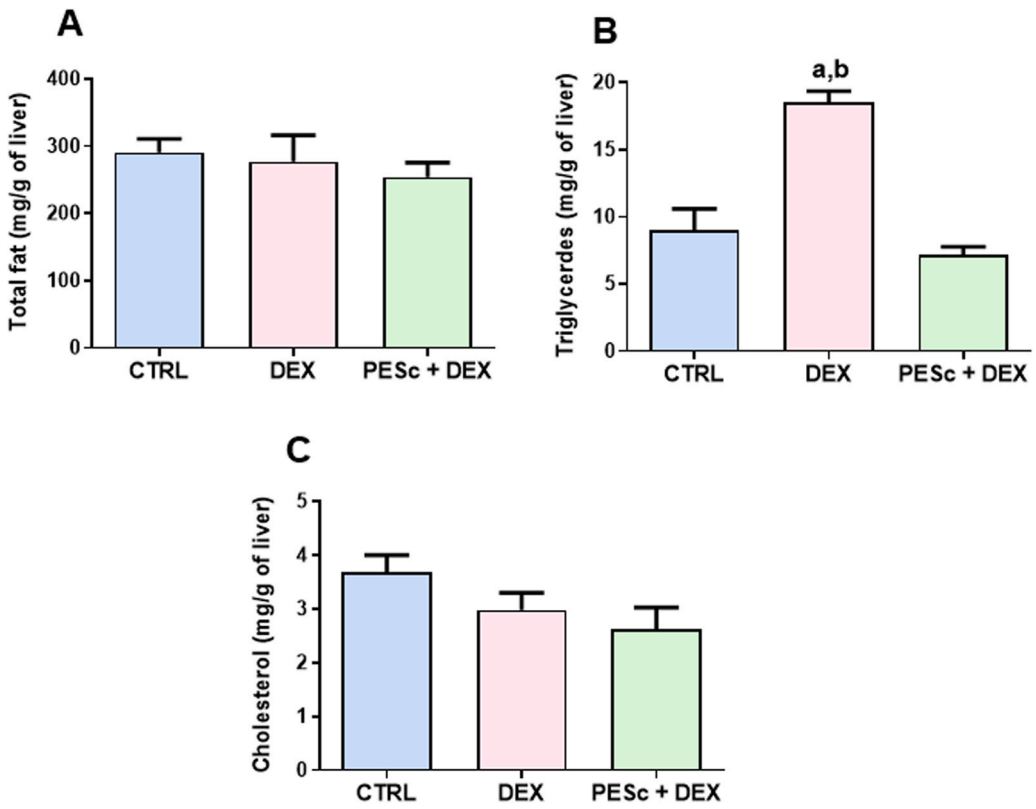

Fig. 4. Effects of the PESc on the liver lipid content. (A) Hepatic Fat, (B) TAG, and (C) total Cholesterol. Values are expressed as mean ± SEM and analyzed using two-way ANOVA followed by the Kruskal-Wallis post hoc test (GraphPad Prism®), $p < 0.05$. (a) Difference compared to the CTRL group; (b) difference compared to the DEX group.

inflammatory cytokine-induced damage [52]. In addition to myricetin, other flavonoids and phenolic compounds in PESc may contribute to its antioxidant capacity [53]. These compounds can modulate the activity of antioxidant enzymes [54,55], which play a critical role in counteracting the redox imbalance triggered by the increased production of reactive oxygen species (ROS) induced by dexamethasone [46].

In vitro studies have shown that increased H_2O_2 production resulting from dexamethasone exposure has deleterious effects on various cellular processes and tissues, including β-cells, leading to impaired insulin secretion [56]. To further explore the mechanisms by which PESc improves metabolic parameters and insulin sensitivity in our T2DM rat model, we investigated the systemic redox response triggered by dexamethasone. To evaluate the extent of oxidative damage caused by dexamethasone-induced T2DM, we measured serum hydroperoxide levels and MDA in these animals. The DEX group exhibited a significant increase in both hydroperoxide and MDA concentrations, which was completely reversed by PESc pretreatment. This reduction in ~~hydroperoxide~~ the levels of these biomarkers may be attributed to the polyphenols present in PESc, as previously reported by our group [15,16]. Next, we investigated the redox response induced by dexamethasone by measuring the activity of key serum antioxidant enzymes, including superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx). DEX-treated animals exhibited a significant increase in SOD activity compared to the control group (non-treated), suggesting an elevated production of ROS, and PESc pre-treatment attenuated this increase. The DEX group also showed elevated CAT activity, but GPx activity remained unchanged compared to the CTRL group, indicating that CAT plays a primary role in detoxifying excess H_2O_2, perhaps from increased activity of SOD, in this model of dexamethasone-induced T2DM.

The redox response to increased ROS is complex, and changes in antioxidant enzyme activity, whether increased or decreased, reflect the extent of oxidative stress [57]. For example, downregulation of these enzymes may result from either inhibited enzyme expression or reduced ROS concentrations [4]. Conversely, upregulation of antioxidant systems can help mitigate oxidative stress and lower the risk of chronic T2DM complications [58]. Elevated SOD activity may lead to H_2O_2 accumulation, which in turn influences the activity of CAT and GPx, enzymes responsible for reducing H_2O_2 [59]. The absence of significant changes in GPx activity may be explained, at least in part, by the fact that total serum GPx might reflect the combined activity of multiple isoforms (GPx1–8), many of which are tissue-specific [60,61] and potentially less responsive to systemic oxidative stimuli than SOD or catalase. In addition, catalase and GPx differ kinetically in H_2O_2 detoxification, with catalase exhibiting a higher Km (lower affinity) and functioning optimally at elevated H_2O_2 concentrations typical of moderate to severe oxidative stress, whereas GPx has a lower Km and efficiently reduces H_2O_2 at low, physiological levels [62–64]. Consistent with these distinctions, the moderate oxidative stress biomarker serum MDA [65] is elevated in our diabetes model and parallels the serum catalase activity profile, but not with GPx activity, which remained unchanged.

Interestingly, while PESc pre-treatment partially reduced CAT activity, it had no effect on GPx activity in diabetic rats. These findings contrast with those of Ravi and co-workers [66], who reported that diabetic animals treated with *S. cumini* fruit peel extract normalized pancreatic SOD, CAT, and GPx activities. This discrepancy may reflect organ-specific differences in the oxidative stress response [67]. Additionally, the composition and concentration of small-molecule antioxidants in plant extracts can vary across the different parts of the plant [68], which may influence the treatment response a given extract. Building on the previously reported antioxidant activity of PESc [16], it is plausible to suggest that the polyphenolic compounds in PESc could contribute to a reduction in hydroperoxides and a partial decrease in

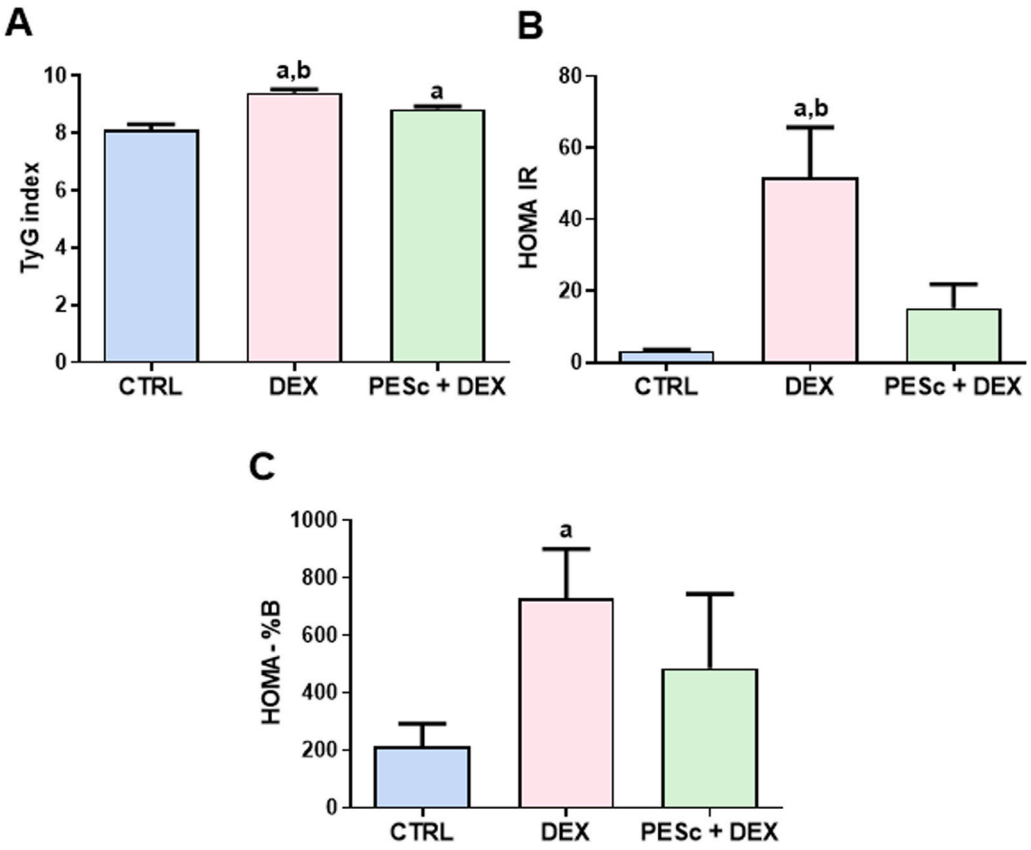

Fig. 5. Effects of the PESc on insulin resistance. (A) TyG index (CTRL n = 8; DEX and PESc + DEX n = 7), (B) HOMA-IR (CTRL and DEX n = 5; PESc + DEX n = 5), and (C) HOMA % B (CTRL and DEX n = 5; PESc + DEX n = 5). Values are expressed as mean ± SEM and analyzed by Kruskal-Wallis ANOVA (GraphPad Prism®), $p < 0.05$. (a) Difference compared to the CTRL group; (b) difference compared to the DEX group.

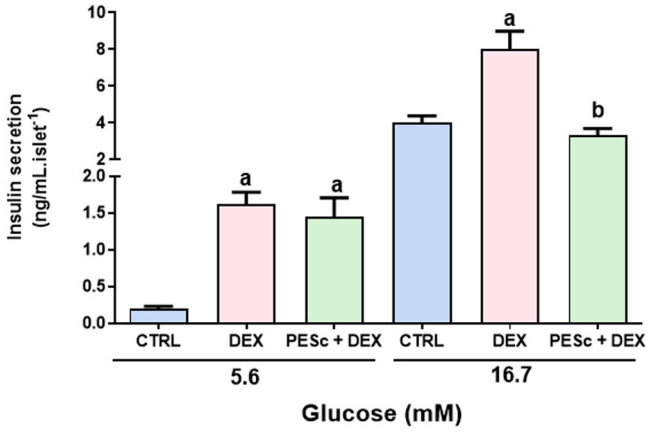

Fig. 6. Effect of the PESc on glucose-stimulated static insulin secretion (GSIS) in pancreatic islets from diabetic rats. Values are expressed as mean ± SEM and were analyzed using ANOVA followed by the Newman–Keuls post-test (GraphPad Prism®), $p < 0.05$. (a) Difference compared to the CTRL group; (b) difference compared to the DEX group. In both glucose concentrations, at least five sets of four islets per group were incubated for 1 h at 37∘C under denoted conditions.

CAT activity. This could occur through direct or indirect effects on reactive oxygen species (ROS) production, particularly H_2O_2. Such redox regulations likely help mitigate the metabolic dysfunction induced by dexamethasone administration.

5. Conclusion

Taken together, these findings demonstrate that PESc improves key metabolic parameters, particularly fasting serum glucose, triglycerides, and insulin levels. After 10 days of treatment, hepatic triglyceride content returned to normal levels. PESc also enhanced insulin sensitivity, as evidenced by improvements in the TyG, HOMA-IR, and HOMA-%B indices. Furthermore, PESc exhibited systemic antioxidant activity by reducing hydroperoxide formation which is reflected in the decreases on catalase activity and MDA. Collectively, these results support PESc as a promising metabolic modulator. Future studies should elucidate the molecular mechanisms underlying PESc effects and evaluate its long-term efficacy and translational potential in models of metabolic dysfunction beyond type 2 diabetes mellitus.

CRediT authorship contribution statement

Everardo Magalhães Carneiro: Resources. **Lucas Martins França:** Project administration. **Karina Ckless:** Writing – review & editing, Data curation. **Nathalee Liberal Xavier Ribeiro:** Writing – original draft, Methodology, Investigation, Formal analysis, Conceptualization. **Ana Paula Gameiro Cappelli:** Supervision, Investigation, Conceptualization. **Perla Lopes Freitas:** Methodology, Investigation. **Bruno Araújo Serra Pinto:** Supervision. **Thamys Marinho Melo:** Visualization. **Franklin Adder Sampaio Muniz:** Methodology, Investigation. **Antonio Marcus de Andrade Paes:** Writing – review & editing, Resources, Funding acquisition, Conceptualization. **Mariana Uchoa da Silva:** Methodology, Investigation. **Karla Frida Torres Flister:** Supervision. **Jonas Rodrigues Sanches:** Methodology, Investigation.

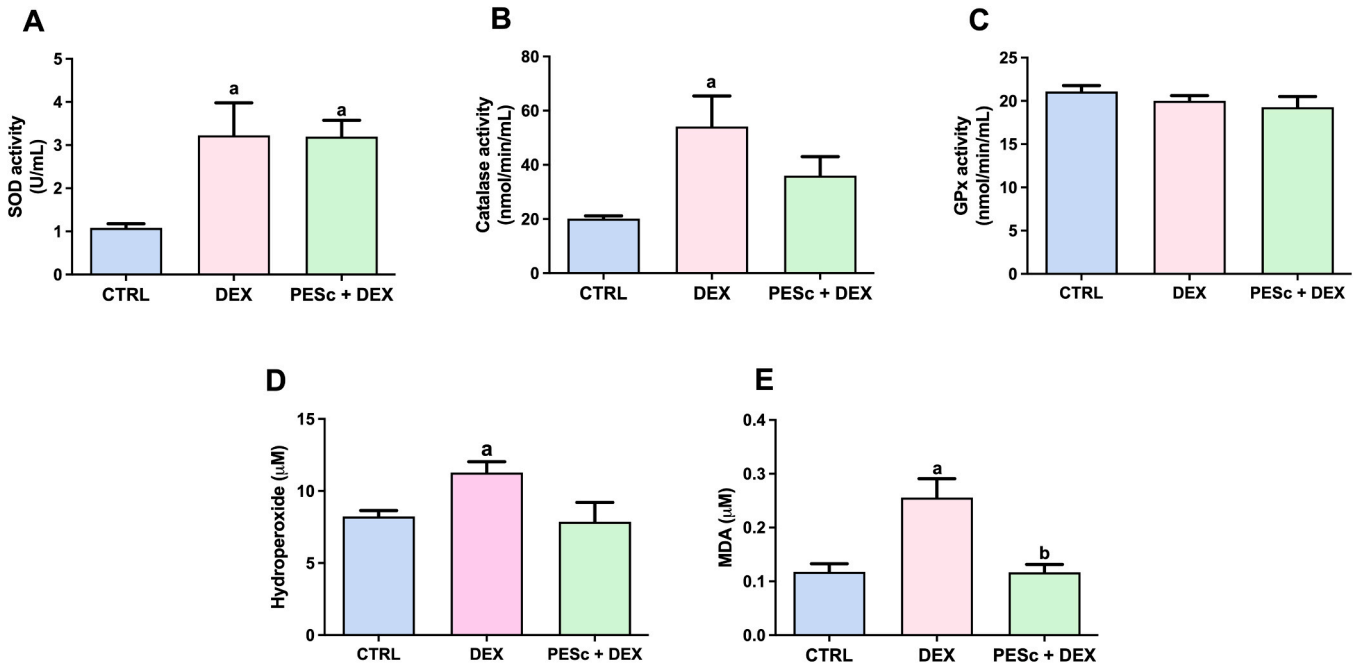

Fig. 7. Effects of the PESc on the systemic redox status (A) Superoxide Dismutase (SOD) (B) Catalase (CAT), (C) Glutathione Peroxidase (GPx) activities, (D) hydroperoxide, and (E) malondialdehyde (MDA) levels. Values are expressed as mean ± SEM and were analyzed using ANOVA followed by the Newman–Keuls post-test (GraphPad Prism®) $p < 0.05$. (a) Difference compared to the CTRL group.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

Data will be made available on request.

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