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# Jaboticaba (*Plinia jaboticaba* (Vell.) Berg) polyphenols alleviate skeletal muscle insulin resistance by modulating PI3K/Akt/GLUT-4 and AMPK signaling pathways in diet-induced obese mice

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## Abstract

Skeletal muscle responds for most of the insulin-stimulated glucose disposal at postprandial state, impacting glucose homeostasis. Polyphenols were shown to prevent obesity-associated glucose intolerance and peripheral insulin resistance in animal models, but the implication of skeletal muscle to these effects is unclear. We investigated the role of polyphenolic extracts from jaboticaba (*Plinia jaboticaba* (Vell.) Berg) (PEJ), a Brazilian native species, on skeletal muscle insulin resistance in diet-induced obese mice. PEJ administration was associated with an increase in skeletal muscle protein content of glucose transporter-4 (GLUT-4) and AMP-activated protein kinase (AMPK) phosphorylated at Thr172. PEJ also reduced skeletal muscle mRNA levels of inflammatory genes nuclear factor- $\kappa$ B (NF- $\kappa$ B), tumoral necrosis factor- $\alpha$  (TNF- $\alpha$ ), interleukin 1 $\beta$  (IL-1 $\beta$ ), and c-Jun N-terminal kinase (JNK). This study demonstrates that polyphenols from jaboticaba may be a valuable therapeutic agent in the management and prevention of obesity-associated metabolic disorders by reducing skeletal muscle obesity-associated insulin resistance and inflammation.

**Keywords** Jaboticaba, Myrtaceae, Obesity, Phenolic compounds, Type 2 diabetes *mellitus*

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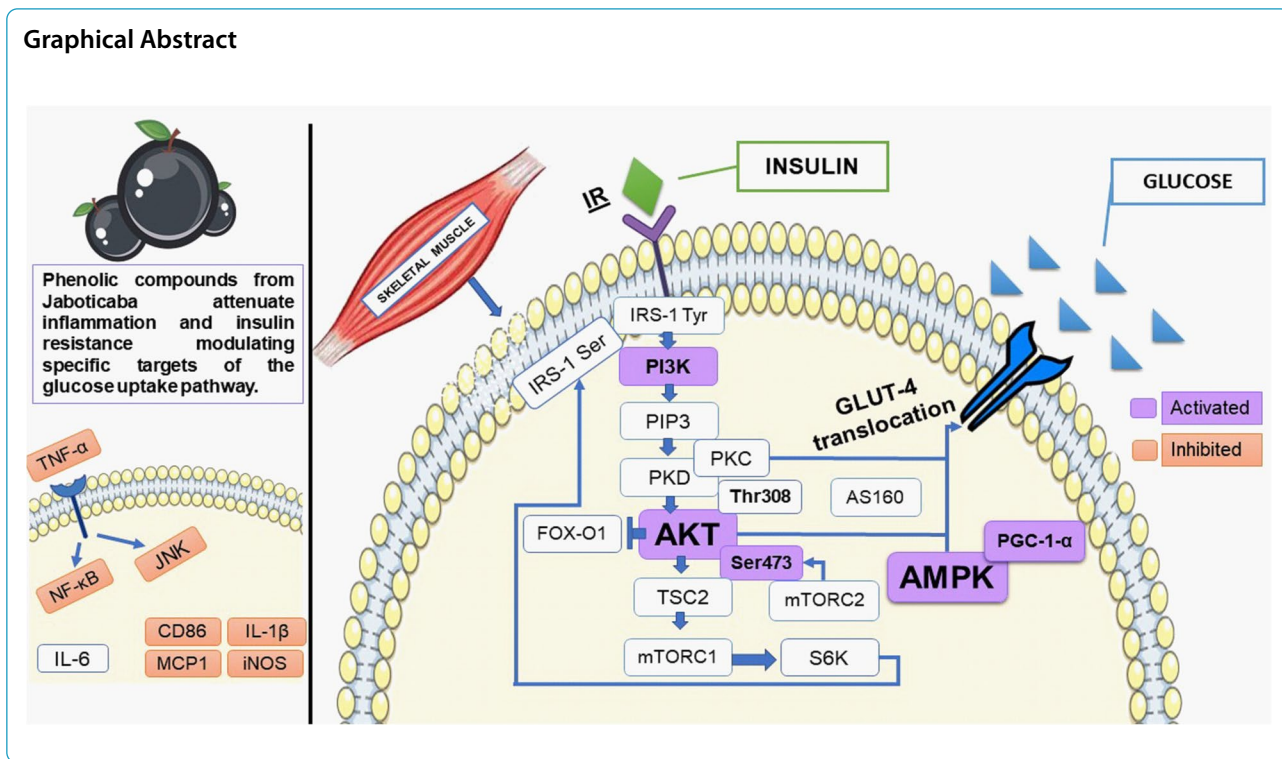
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### Introduction

Visceral obesity is a serious and growing public health problem. Worldwide obesity prevalence has tripled since 1975. In 2016, more than 1.9 billion people over 18 years old were overweight, among which 650 million were obese. In addition, more than 350 million children and adolescents aged between 5 and 19 years are overweight or obese (WHO 2018). Visceral obesity is a major risk factor for the development of several chronic diseases such as insulin resistance and type 2 diabetes (T2DM), metabolic disorders characterized by hyperglycemia due to failures in insulin action, secretion, or both. Skeletal muscle is responsible for approximately 75% of insulin-stimulated glucose disposal (Papaetis et al. 2015). Therefore, insulin resistance defined as the inability of this hormone to promote glucose uptake in this organ has a major negative impact on glucose homeostasis (Jagathan et al. 2018; Latha & Daisy 2011).

The mechanisms by which visceral obesity promotes insulin resistance are not completely defined, but they seem to involve the development of chronic and systemic low-grade inflammatory process. Indeed, excessive accumulation of fat in the visceral white adipose depots is associated with the recruitment, infiltration and polarization of macrophage to a proinflammatory profile. These cells along with hypertrophied adipocytes produce several proinflammatory cytokines such as interleukin 6 (IL-6), and tumor necrosis factor-alpha (TNF- $\alpha$ ) and IL-1b,

among others that were previously shown to negatively impact several steps in the insulin intracellular cascade (Jung & Choi 2014; Verma & Hussain 2017). In addition to inflammation, other factors connecting visceral obesity to insulin resistance are lipotoxicity, endoplasmic reticulum stress, mitochondrial dysfunction, and oxidative stress (Wondmkun 2020).

Because of its major contribution to insulin-stimulated glucose disposal, skeletal muscle has become an interesting target to counteract insulin resistance and T2DM development in obese patients (Boström et al. 2012; Samuel & Shulman 2016). In fact, lifestyle changes such as the regular practice of physical activity, and healthy eating habits such as regular consumption of whole grains, fruits, and vegetables, can reduce insulin resistance and T2DM. The protective and beneficial role of bioactive molecules from fruits and vegetables in human health has attracted considerable attention in recent years. Studies suggest that these bioactive compounds (e.g., polyphenols and carotenoids) can reduce the risk of developing non-communicable chronic metabolic diseases (Cui et al. 2007; Del Rio et al. 2013).

Polyphenols can attenuate obesity-induced inflammation and insulin resistance by inhibiting the production of inflammatory cytokines, as well as by reducing oxidative stress, dyslipidemia and lipotoxicity (Gothai et al. 2016). The Brazilian flora is characterized by a wide biodiversity, where several non-conventional edible

plants belonging to Myrtaceae family have an ecological relevance (Donado-Pestana et al. 2018). Previously, our group has chemically characterized polyphenolic extracts from jaboticaba (*Plinia jaboticaba* (Vell.) Berg) (PEJ), belonging to Myrtaceae species, as being rich in proanthocyanidins, anthocyanins and ellagitannins (Alezandro et al. 2013), compounds with well-recognized anti-inflammatory and antioxidant properties. Recently, Moura et al., (2021) showed that PEJ decreased insulin resistance in white adipose tissue, skeletal muscle, and liver; however, the molecular mechanism and the cellular signaling pathways involved in these biological effects are still unknown. Here, we aimed to investigate the effect of PEJ on specific targets in the glucose uptake and inflammatory pathways in skeletal muscle, elucidating mechanisms of amelioration on insulin resistance in diet-induced obese mice.

## Material and methods

### Preparation of polyphenolic extracts from jaboticaba (PEJ)

Sabara jaboticaba (*Plinia jaboticaba* (Vell.) Berg) fruits were acquired from a local market (São Paulo Central Market, CEAGESP, São Paulo, Brazil), which in turn originated from a local producer localized at the Jaboticabal city (State of São Paulo, Brazil). Fruits were sanitized by immersion in a sodium hypochlorite solution (1%), lyophilized, powdered in an analytic mill (Quimis-6298A21), and stored at -20 °C. The PEJ was obtained through a hydromethanolic extraction of the jaboticaba fruit powder, as previously described by Moura et al., (2021). Briefly, a methanol/water/acetic acid solution (70:30:0.5 v/v/v) was used for extraction at a solid-to-solvent ratio of 1:25 (m/v) and shaking for 2 h at 4 °C. The extract was vacuum-filtered, and the residue re-extracted twice for 30 min each. Next, the extract was concentrated by roto-evaporation and the polyphenolic-enriched fraction was obtained using an octadecylsilane (C18) column (Supelclean™ LC-18, Supelco) preconditioned with methanol and distilled water. Aqueous extract was loaded onto the column and eluted with methanol. Finally, solvent was evaporated and PEJ was resuspended in water. Phenolic characterization of PEJ is provided in Supplementary Table S1.

### Animals and experimental design

Male C57BL/6 J mice aged eight weeks (average weight 26 ± 2 g) were housed, cared for and handled as previously described (Moura et al. 2021) in conformance with the experimental procedures approved by the Ethical Committee for Animal Research of the Faculty of Pharmaceutical Sciences of the University of São Paulo (CEUA/FCF/522). After one week of adaptation to the housing conditions, mice were fed a standard (Chow)

diet ( $n=6$  animals) or a high-fat-sucrose (HFS) diet, ( $n=18$ ) for 14 weeks and water ad libitum for both groups. The chow diet was an AIN-93 M diet containing 3.8 kcal/g, being 13.6% as protein, 10.7% as lipids and 75.7% as carbohydrates. HFS diet was manually prepared and contained 4.6 kcal/g, 20% from protein, 39% from lipids and 41% from simple carbohydrates (sucrose). After this period, mice in the HFS group remained with the same diet and were divided into three groups of six animals; namely HFS group, receiving daily gavage of water; PEJ1 group, receiving daily gavage of 50 mg gallic acid equivalent (GAE)/kg; and PEJ2 group receiving daily gavage of 100 mg of GAE/kg. PEJ doses were defined according to previous studies by our group (Alezandro et al. 2013; Moura et al. 2021). The Chow group remained with the same standard diet and received water by daily gavage. Water and PEJ were administered to the animals for 14 weeks. Animals were euthanized by cardiac puncture under anesthesia (isoflurane) and the gastrocnemius muscle was collected, weighed and stored at -80 °C.

### Protein analysis by immunoblotting

Gastrocnemius muscle fraction (45–55 mg tissue) was homogenized (T10, Ultra-Turrax®) in 400 µL of ice-cold extraction in lysis buffer (50 mM HEPES, 40 mM NaCl, 50 mM NaF, 2 mM EDTA, 10 mM sodium pyrophosphate, 10 mM sodium glycerophosphate, 1.5 mM sodium orthovanadate, 10 mM sodium β-glycerophosphate, and a protease inhibitor cocktail (cOmplete Mini, Roche)). Samples were centrifuged at 12,000 g for 20 min at 4 °C. Protein concentration was measured using a commercial kit (Pierce BCA, Thermo Scientific, Rockford, USA). Proteins were denatured by heating in Laemmli buffer, separated on 10–12% SDS-PAGE, and transferred to PVDF membranes (Merck Millipore, Massachusetts, USA). Membranes were incubated with primary antibodies of interest (Table 1). Membranes were washed and incubated with peroxidase-conjugated secondary antibody and revealed by chemiluminescence (ECL, GE Healthcare, USA). Bands densitometry was determined using the Image J program (National Institute of Health, Illinois, USA).

### Gene expression analysis by quantitative PCR

RNA was extracted from muscle (30–40 mg) using Trizol (Life Technologies, Thermo Scientific, Waltham, MA, USA). RNA concentration was measured using NanoDrop spectrophotometer (Thermo Scientific, Waltham, MA, USA). Synthesized cDNA was mixed with the primer sequences of targets of interest (Table 1), and reactions were performed with SYBR® Green JumpStart™ Taq ReadyMix™ (Sigma Aldrich, St. Louis, MO) using Rotor-Gene (Qiagen, Valencia, CA). Quantification of

**Table 1** Antibodies for western blotting and primer sequences for real-time PCR

Antibody	Catalog number	Manufacturer
pAMPK Thr172	#2531	Cell Signalling Technology
Total AMPK	#5831	Cell Signalling Technology
GLUT-4	MA5-17176	Invitrogen
Akt Total	#9272	Cell Signalling Technology
p-Akt Ser473	#9271	Cell Signalling Technology
p-Akt Thr308	#4056	Cell Signalling Technology
TLR-4	48–2300	Invitrogen
p-S6 Ser240/244	#5364	Cell Signalling Technology
p-NF- $\kappa$ B Ser 536	#3033	Cell Signalling Technology
FOXO1	#97635	Cell Signalling Technology
PGC-1 $\alpha$	#SC-13067	Santa Cruz Biotechnology
Tubulin	sc-5286	Santa Cruz Biotechnology
$\beta$ -actin	#3700	Cell Signalling Technology
Primer	Forward	Reverse
IRS	TTCGATGTCCACCCAGCTC	GCTATTGGCCACCGAACGGG
PI3K	TGCTGAGAAGGACACGTGGG	TGCTCCATCAACGGGGTG
PKC $\alpha$	TCGCCAACAGGGAAGGGTAAG	GGGCAGTTTGTATGGCAGC
AMPK	GCAAAGTGAAGACTACCAGGTG	CGCGCTCCACCTCTTCAAC
NF- $\kappa$ B	TCAGAACTCTGCAGGTGAGACC	CAGAACTCTGCAGGTGAGACC
TNF- $\alpha$	GGGCAGTTAGGCATGGGATG	TACTACGACGTGGGCTACAG
JNK	TCAGAAGCAGAAGCCCCACC	ACGGCTGCCCTTATGACTC
iNOS2	TTCTCAGCCACCTTGGTGAAG	ACTCCGTGGAGTGAACAAGACC
IL-1 $\beta$	GCCACCTTTTGACAGTGATGAG	TGATCTGCTGCTGCGAGATT
F4/80	GCCACGGGGCTATGGGATGC	TCCCGTACCTGACGGTTGAGCA
CD86	CCCAGCAACACAGCCTCTAA	ACTCTGCATTTGGTTTGTCTGA
VEGF- $\alpha$	ACTGGACCTGGCTTACTG	TGAACCTGATCACTTCATGGGAC

*pAMPK Thr 172* Phosphorylated adenosine monophosphate-activated protein kinase, *GLUT-4* glucose transporter type 4, *pAKT Ser473/Thr308* Phosphorylated protein kinase B, *TLR-4* Toll-like receptor type 4, *p-S6 Ser240/244* Ribosomal protein S6 kinase, *p-NF- $\kappa$ B Ser 536* Nuclear transcription factor-kappa B, *FOXO1* forkhead box protein O1, *PGC-1 $\alpha$*  Proliferator-activated receptor- $\gamma$  co-activator 1 $\alpha$ , *IRS* Insulin substrate receptor, *PI3K* phosphoinositide 3-kinase, *PKC* protein kinase C, *AMPK* AMP-activated protein kinase, *MAPK* mitogen-activated protein kinase, *NF- $\kappa$ B* nuclear factor kappa-light-chain-enhancer of activated B cells, *TNF- $\alpha$*  tumor necrosis factor- $\alpha$ , *JNK* c-Jun N-terminal kinase, *iNOS2* inducible nitric oxide synthase 2, *IL-1 $\beta$*  interleukin 1 beta, *F4/80* CD86, cluster of differentiation 86, vascular endothelial growth factor alpha (VEGF- $\alpha$ )

gene expression was performed using the  $\Delta\Delta$ Ct method and expressed relatively to VEGF expression as an internal standard (Livak & Schmittgen 2001).

#### Enzyme-linked immunosorbent assay (ELISA)

Skeletal muscle homogenates (45–55 mg) were obtained as described previously in immunoblotting section. Interleukin-6 (IL-6), and monocyte chemoattractant protein-1 (MCP-1) were measured by ELISA (DuoSet ELISA<sup>®</sup>, R&D Systems, Minneapolis, MN, USA).

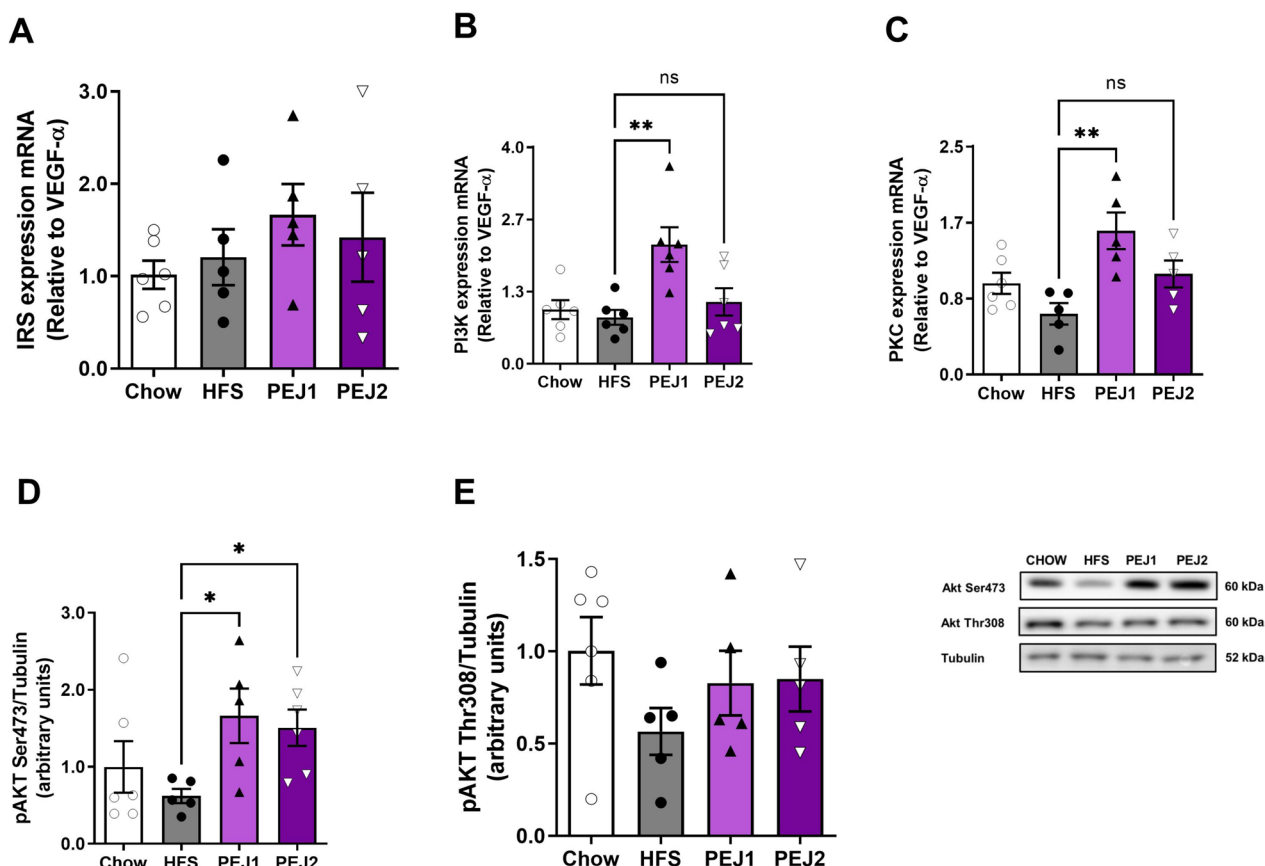
#### Statistical analysis

Data were analyzed regarding the nature of their distribution by the Shapiro–Wilk test. Groups were compared by analysis of variance (ANOVA) with Tukey adjustment (parametric) or Kruskal–Wallis with Dunn test (non-parametric). Statistical significance was set at a  $p$ -value < 0.05. Analysis was performed using GraphPad

Prism software (GraphPad Software, version 6.0, La Jolla, CA, USA).

#### Results and discussion

In this study we provide new insights into molecular mechanism and the intracellular signaling pathways regulated by PEJ in the skeletal muscle of diet-induced obese mice. Ellagitannins, proanthocyanidins, anthocyanins (cyanidin and delphinidin derivatives), and free ellagic acid, have been identified as the major phenolic compounds found in PEJ (Supplementary Table S1), which were showed to exert biological actions reducing the risk of metabolic disorders (Del Rio et al. 2010). Both PEJ doses induced a slight, although not significant, increase in insulin receptor substrate-1 (IRS-1) transcription (Fig. 1A). PI3K and PKC gene expression were significantly increased by PEJ1 (Fig. 1B, C), and p-Akt Ser473 protein content was significantly increased in both PEJ



**Fig. 1** Gene expression of IRS (a), PI3K (b), and PKC (c), and representative immunoblots of p-Akt (Ser473 (d) and Thr308 (e)) from gastrocnemius muscle of mice fed with high-fat-sucrose diet (HFS group) or standard diet (chow group) and receiving water or phenolic-rich extracts from jaboricaba at two doses (PEJ1 and PEJ2 groups). Data are means ± SEM from each treatment (n = 5–6). \* (p < 0.05) vs. HFS, \*\* (p < 0.01) vs. HFS

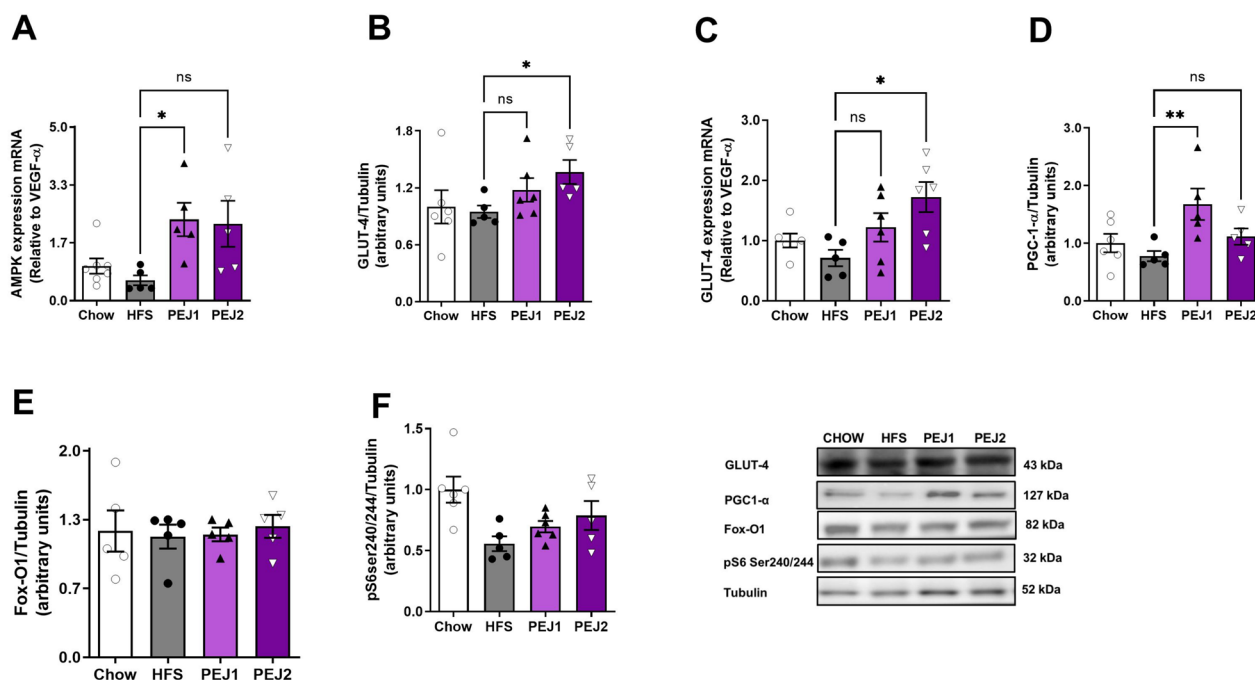
groups (Fig. 1D). On the other hand, the protein content of p-Akt Thr308 did not change significantly after treatment with PEJ (Fig. 1E). As it is known, skeletal muscle exhibits a fundamentally key role in the maintenance of glucose homeostasis; however, in an obesity condition, nutrient overload leads to insulin resistance in this organ. We have reported that PEJ improved glucose homeostasis by improving glucose tolerance and attenuating hyperglycemia and hyperinsulinemia in our earlier study (Moura et al. 2021).

These PEJ protective properties may be associated with several mechanisms of glycemia regulation. In fact, here we provide evidence that PEJ improves glucose homeostasis by enhancing insulin sensitivity and intracellular signaling in the skeletal muscle of obese mice; specifically, PEJ was able to increase the PI3K-Akt/PKC pathway. Phosphatidylinositol 3-kinase (PI3K) is activated through tyrosine phosphorylation of insulin receptor substrate-1 (IRS-1) when insulin binds to its receptor. The activation of PI3K increases the intracellular PIP3 levels as well as the recruitment, phosphorylation and activation of Akt

(Ueda-Wakagi et al. 2015). Akt is a serine/threonine-protein kinase that is a critical mediator of insulin actions promoting GLUT-4 translocation, muscle glucose uptake and glycogen synthesis in the skeletal muscle (Rathinam & Fitzgerald 2017; Sayem et al. 2018). On the other hand, polyphenols have also been demonstrated to exert their biological actions by interfering in the protein kinase C (PKC) signaling pathway. This regulation by polyphenols is isoform-dependent and the activation or inhibition of PKD by a particular polyphenol depend on Ca<sup>2+</sup> ions, cofactors, cell and tissue types or in the presence of membrane (Das et al. 2016).

In order to find other factors mediating glucose metabolism, we examined the modulation of AMPK, GLUT-4, PGC-1-α, FOXO1, and S6. As shown in Fig. 2A, PEJ administration increased gene expression of AMPK, a major regulator of intracellular energy homeostasis, and increased gene expression and protein content of GLUT-4, a key glucose transporter in muscle cells (Fig. 2B, C). Moreover, PEJ1 increased protein content of PGC-1-α (Fig. 2D); however, we did not observe significant



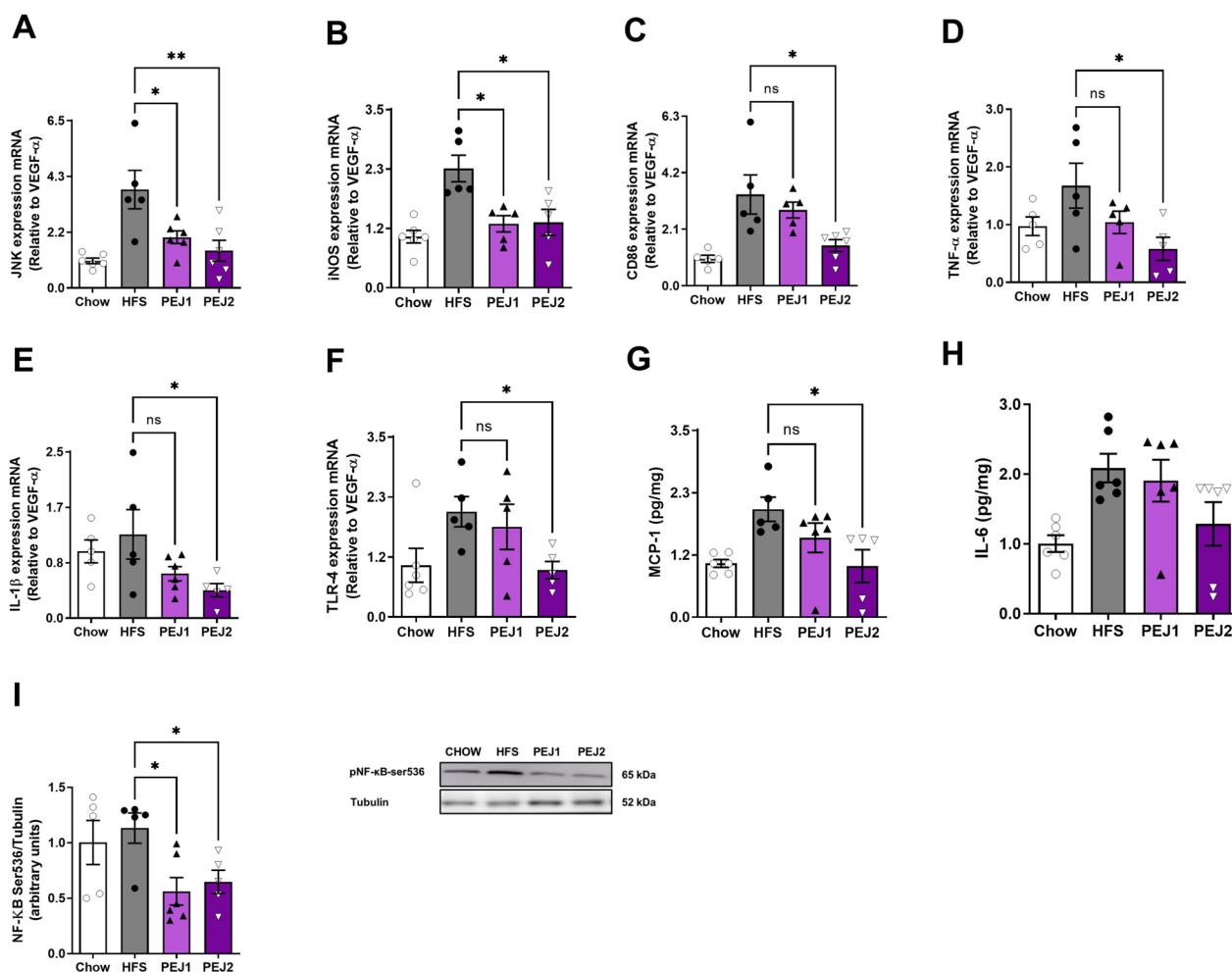


**Fig. 2** Gene expression of AMPK (a), representative immunoblots and gene expression of GLUT-4 (b, c), and representative immunoblots of PGC1-α (d), Fox-O1 (e), and phospho-S6 protein (Ser240/244) (f) from gastrocnemius muscle of mice fed with high-fat-sucrose diet (HFS group) or standard diet (chow group) and receiving water or phenolic-rich extracts from jaborcaba at two doses (PEJ1 and PEJ2 groups). Data are means ± SEM from each treatment (n = 5–6). \* (p < 0.05) vs. HFS, \*\* (p < 0.01) vs. HFS

differences in Fox-O1 and p-S6 Ser240/244 protein contents among groups (Fig. 2E and F). Interestingly, the improvement in glucose homeostasis induced by PEJ can also be associated with the activation of the AMPK pathway in the skeletal muscle as evidenced by the increased AMPK transcription, an essential metabolic and energy regulator. Evidence suggests that AMPK also stimulates GLUT-4 translocation to the plasma membrane (Shrestha et al. 2021). Indeed, Peng et al. showed that chicoric acid, a polyphenol from a subclass of hydroxycinnamic acid, promoted insulin-independent glucose uptake and Akt phosphorylation by regulating AMPK in cultured C2C12 myotubes (Peng et al. 2019). Previous studies have reported that polyphenols obtained from native species attenuated insulin resistance and increased insulin sensitivity in key metabolic tissues (liver, skeletal muscle, and adipose tissue) through the activation of AMPK/PI3K/Akt signaling pathways (Donado-Pestana et al. 2021; Naowaboot et al. 2018). Along with AMPK, PEJ also increased the expression of PGC1-α, which is primarily involved in the regulation of oxidative metabolism and mitochondrial biogenesis in skeletal muscle. These findings suggest that PEJ may improve insulin sensitivity and glucose homeostasis by enhancing mitochondrial biogenesis and function. Similarly to PEJ, daidzein, a polyphenol found naturally in soybeans and other

legumes, protected against chronic diseases by activating PGC1-α, AMPK and SIRT1 in muscle-related mitochondrial biogenesis (Yoshino et al. 2015).

Since chronic activation of inflammatory pathways contributes to obesity-related insulin resistance in skeletal muscle, we evaluated whether PEJ modulates inflammation induced by HFS. Both PEJ1 and PEJ 2 doses significantly reduced JNK, iNOS, and CD86 gene expression (Fig. 3A-C). Furthermore, TNF-α, IL-1β, and TLR-4 gene expression and MCP-1 levels were decreased significantly by PEJ2 in comparison to the HFS group (Fig. 3D-G). IL-6 protein content did not differ significantly among HFS-fed animals (Fig. 3H). Finally, animals receiving both PEJ doses had a significant decrease of NF-κB phosphorylated at Ser 536 (Fig. 3I). During obesity progression, the expansion of adipose deposits among and/or surrounding muscle fibers (intermuscular adipose tissue/perimuscular adipose tissue, IMAT/PMAT) and the increased infiltration and polarization of immune cells (e.g., macrophages and T cells) in these fat depots lead to an exacerbated local production of inflammatory mediators. This finding along with enhanced production of pro-inflammatory cytokines and chemokines (e.g., IL-6 and TNF-α) by inflamed myocytes, may lead to impairments in insulin signaling and sensitivity in muscle (Wu et al. 2017). The anti-inflammatory effects mediated by PEJ



**Fig. 3** Gene expression of JNK (a), iNOS (b), CD86 (c), TNF- $\alpha$  (d), IL-1 $\beta$  (e), and TLR-4 (f), and levels of MCP-1 (g) and IL-6 (h), and representative immunoblots of p-NF- $\kappa$ B (Ser536) (i) from the gastrocnemius muscle of mice fed with high-fat-sucrose diet (HFS group) or standard diet (chow group) and receiving water or phenolic-rich extracts from jaboticaba at two doses (PEJ1 and PEJ2 groups). Data are means  $\pm$  SEM from each treatment ( $n=5-6$ ). \* ( $p < 0.05$ ) vs. HFS, \*\* ( $p < 0.01$ ) vs. HFS

may explain the improvement in the response to insulin action in our animal model. Supporting this notion, Dragano et al. showed that supplementation with jaboticaba peel rich in anthocyanin reduced insulin resistance in mice fed with a high-fat diet by attenuating inflammation in the liver evidenced by the reductions in IL-1 $\beta$  and IL-6 expression and phosphorylated I $\kappa$ B- $\alpha$  protein levels (Dragano et al. 2013).

**Conclusion**

In summary, PEJ demonstrated beneficial properties against obesity-induced insulin resistance in skeletal muscle of diet-induced obese mice. These properties were mediated by regulation of specific targets in the insulin-signaling pathway including Akt Ser473, PI3K, and GLUT-4, as well as AMPK pathway. PEJ also increased PGC1- $\alpha$ , probably related to oxidative metabolism

enhancement in the skeletal muscle. Moreover, PEJ also acted against obesity-associated inflammation, reducing cytokines and NF- $\kappa$ B levels and inflammatory genes transcription, improving glycemic homeostasis.

**Supplementary Information**

The online version contains supplementary material available at <https://doi.org/10.1186/s43014-024-00230-y>.

**Additional file 1: Supplementary Table S1.** Phenolic characterization of the PEJ. **Supplementary Table S2.** Diet composition. **Supplementary Figure S1.** Body weight (a), energy intake (b), and glucose metabolism: Weekly variation of fasting blood glucose, FBG (c-e), intraperitoneal insulin tolerance test, ipITT (f-g), oral glucose tolerance test, oGTT (h-k) and homeostatic model assessment (HOMA-IR) (l) of mice fed with high-fat-sucrose diet (HFS group) or standard diet (chow group) and receiving water or phenolic-rich extracts from jaboticaba at two doses (PEJ1 and PEJ2 groups). Data are means  $\pm$  SD from each treatment. n.s: not significant, \* ( $p < 0.05$ ), \*\* ( $p < 0.01$ ), \*\*\* ( $p < 0.001$ ), # Chow vs HFS ( $p < 0.005$ ), ##

HFS vs PEJ1 and PEJ2. (Reprinted from Food Research International, Vol 143, Moura et al., Long-term supplementation with phenolic compounds from jaboticaba (*Plinia jaboticaba* (Vell.) Berg) reduces adiposopathy and improves glucose, lipid, and energy metabolism, 17 pages, 2021, with permission from Elsevier).

**Additional file 2.**

**Additional file 3.**

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### Authors' contributions

ÉVMP, MHCM, LR, RR, ÉC, and CMDP, performed experiments. ÉVMP and CMDP analyzed data. ÉVMP and MIG conceived and designed the study. ÉVMP, CMDP, WTF, and MIG, wrote the paper. WTF, and MIG, checked and revised the paper.

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### Availability of data and materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

### Declarations

#### Ethics approval and consent to participate

The study was reviewed and approved by the Ethical Committee for Animal Research of the Faculty of Pharmaceutical Sciences of the University of São Paulo (CEUA/FCF/522). A, USA. All experiments followed the guide for the care and use of laboratory animals.

#### Consent for publication

Not applicable.

#### Competing interests

The authors declare that they have no known competing interests.

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