



Quinoa and Chia Modulate AMPK/PPAR- γ Signaling in High-Fat Diet-Induced Obesity Rat Model

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Abstract

Obesity is one of the principal reasons behind a wide range of metabolic diseases and dramatic health complications. Recent studies shed the light on chia (*Salvia hispanica* L., Lamiaceae) and quinoa (*Chenopodium quinoa* Willd., Amaranthaceae) seeds and identified them as products of utmost health benefits. The present study was designed to explore the molecular mechanisms of the hydroalcoholic extract of those seeds in weight management. Rats were divided randomly into two main groups: control and treated. The control groups received regular chow diet, high-fat diet, and green tea. The treated groups received high-fat diet and chia or quinoa extracts. Results revealed that the seeds showed hepatoprotective effects and anti-inflammatory and antioxidant activities, and modulated leptin, adiponectin, serum lipid, and glycemic profiles. Effects are further consolidated by normal hepatic tissue architecture upon histopathological examination. Moreover, modulation of peroxisome proliferator-activated receptors- γ transcriptional activity via activation of 5'AMP-activated protein kinase and suppression of nuclear expression of sterol regulatory element-binding protein-1c in obese rats as compared to green tea were demonstrated. Characterization of the major secondary bioactive metabolites was done using HPLC/PDA/ESI-MS/MS. Our study advocates evidence-based study on nutrition and health claims on the use of chia and quinoa extracts as nutraceutical supplements for promoting weight wellness and alleviating its related metabolic disorders.

Keywords Antioxidants · Metabolic diseases · Metabolic syndrome · Phenolics · Obesity · Weight loss

Introduction

Obesity and metabolic syndrome represent chief universal public health challenges. Healthcare professionals can revisit it as “the world’s new syndrome.” We as humans have evolved effective physiological mechanisms to protect against weight loss,

but failed to be protected against weight gain in times of food abundance (Hill and Peters 1998). Moreover, due to sedentary lifestyle and risky behaviors such as unhealthy eating, smoking, and excessive alcohol, the world is confronted more than ever with the noncommunicable diseases (NCDs), including heart disease, stroke, cancer, diabetes, and chronic lung disease (Emanuela et al. 2012). Additionally, several studies suggested the link between metabolic syndrome and the etiology of certain disease such as cancer (Rasheed et al. 2022) and cognitive impairments manifested in Alzheimer’s disease (Vanhanen et al. 2006). The diagnosis of metabolic syndrome is confirmed when patients meet at least three of the following five criteria: hypertension, abdominal obesity, high triacylglyceride (TG), low high-density lipoprotein-cholesterol (HDL-C), and insulin resistance (IR) related to type 2 diabetes mellitus (T2DM) (Ascaso et al. 2003). Noteworthy, reducing body weight by 5–10% greatly lowers metabolic syndrome components, and hence the risk of fatal comorbidities (Magkos et al. 2016).

Recently, the introduction of healthy lifestyle has gained wide popularity against the battle of many chronic diseases including obesity and related disorders. Unfortunately, dieting and exercising fail in some individuals. Pharmacological treatment should only be advised in case of body mass index (BMI) > 30

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or BMI ≥ 27 with comorbidity (Apovian et al. 2015). Consequently, synthetic drugs, especially appetite suppressors acting on the CNS and bariatric surgeries, in many instances, result in several complications (Fassina et al. 2015). Henceforth, safe pharmacological interventions become dictated.

Natural products incorporated in either the foodstuffs or pharmaceutical products are offering an alternative approach for obesity management with fewer side effects (Kazemipoor et al. 2012). Those are mostly of plant origin, including seeds, grains, vegetables, fruits, and herbs. The biological effects of these natural products are attributed to the abundance of active redox chemicals (antioxidants), fibers, and unsaturated fatty acids. Noteworthy, grape seed extract (Liu et al. 2020a, b), fenugreek seeds (Yao et al. 2020), and green coffee beans (Murase et al. 2011) are widely used in weight management. Endowed with anti-inflammatory, antioxidant, lipid profile adjustment, and antidiabetic effects, chia, *Salvia hispanica* L., Lamiaceae (Scapin et al. 2016), and quinoa, *Chenopodium quinoa* Willd., Amaranthaceae (Noratto et al. 2019), are medicinal plants of high nutritive value, ascribed with many health benefits (Kulczyński et al. 2019). The seeds are a rich source of fibers, polyphenols, and omega-3 fatty acids that reduce inflammation and oxidative stress, and enhance cognitive functions (De Falco et al. 2017; Liu et al. 2020a, b).

The peroxisome proliferator-activated receptors (PPARs) are transcription factors that modulate a wide array of physiological processes comprising cell growth, differentiation, membrane lipid synthesis/turnover, and homeostasis (Ahmed et al. 2007), highly expressed in muscles (Barish et al. 2006). Moreover, these receptors regulate the expression of genes involved in fatty acid metabolism and obesity (Ahmed et al. 2007). AMP-activated protein kinase (AMPK) is an imperative energy sensor in cells (Chanda et al. 2009) and its activation stimulates fatty acid oxidation in liver and heart, inhibits hepatic lipogenesis and adipocyte differentiation, and enhances glucose uptake by muscles (Lage et al. 2008). Growing body of evidence suggests that PPAR- γ agonists modulate the activity of (AMPK), probably via SIRT 1 (a protein that plays a key role in hepatic lipid metabolism) activation (Chanda et al. 2009).

The present study was designed to investigate the potential therapeutic merits of chia and quinoa seeds in weight loss and comparing their effects with green tea as a reference herb. Mechanistic insights into the AMPK- α modulating PPAR- γ pathway regulating lipogenesis, adipogenesis, and inflammation have also been explored on the phenolic profiles of both plants.

Materials and Methods

Plant Material

Fresh seeds (1 kg) of chia, *Salvia hispanica* L., Lamiaceae, and quinoa seeds, *Chenopodium quinoa* Willd., Amaranthaceae, were obtained from Agricultural Genetic Engineering

Research Institute, Cairo, Egypt, in April 2018. Taxonomist Dr. Mahmoud Zidan kindly authenticated the seeds. Specimens of the identified seeds were deposited at the herbarium of the Department of Pharmaceutical Biology, Faculty of Pharmacy and Biotechnology, German University in Cairo (Chia: GUCPHBL1 2019; Quinoa: GUCPHBL2 2019).

Initially, defatting of seeds was done with hexane (Sigma Aldrich, Munich, Germany) followed by exhausting with 75% ethanol-water until complete extraction. The supernatant was filtered on #4 Whatman filters and then evaporated under reduced pressure at temp. 40 °C using a rotavapor (Buchi, R-210, Switzerland). They yielded semisolids of 6.5 w/w% for chia and 9.5 w/w% for quinoa. Similarly, hydroalcoholic extract was obtained from 2 kg of green tea leaves. The amount of total phenolics was determined quantitatively using Folin-Ciocalteu's reagent and expressed as gallic acid equivalent per gram of dry weight of the plant extract (mg GAE/g DW). Flavonoids were measured in milligram per gram quercetin equivalent per gram of dry weight of the extract using the previously mentioned adapted aluminum chloride, Merck (Darmstadt, Germany) colorimetric assay (Aryal et al. 2019).

Animals

Adult male white albino Wistar rats, weighing 150–200 g, were obtained from the National Research Centre (Cairo, Egypt). They were housed in standard polypropylene cages, where each cage contained 6 rats and were housed under appropriate conditions of temperature (25 ± 2 °C), humidity (60–70%), and light (12-h dark/light cycles). The animals were left for 1 week before experimental intervention for acclimatization at the GUC animal house. Free access to food and water was allowed, prior to the dietary manipulation.

Experimental Design

Based on our preliminary study, dose selection was conducted, where the optimum doses for chia and quinoa hydroalcoholic extracts were selected for statistical analysis fulfilling safety criteria and weight loss results. Accordingly, chia dose of 200 mg/kg b.w./day and quinoa dose of 200 mg/kg b.w./day were selected. As shown in Fig. S1, animals were divided into five groups ($n = 6/\text{group}$) along the 6 weeks.

Group I: normal food diet (NFD) were fed normal food (chow) diet and saline.

Group II: high-fat diet (HFD) animals were fed high fat diet and saline.

Group III: (HFD + green tea) animals on HFD, received green tea extract in dose 250 mg/kg/day.

Group IV: (HFD + quinoa) animals on HFD, received quinoa in dose 250 mg/kg/day dissolved in saline (Ghahremanloo et al. 2018), and

Group V: (HFD + chia) animals on HFD, received chia in dose 250 mg/kg/day dissolved in saline (Apoorva et al. 2020).

All groups received treatments orally. Animals were fasted overnight and anesthetized with diethyl ether (Camlab, UK). Twenty-four hours after the last dose, rats were sacrificed, and blood samples were collected from the animal's venous sinus using capillary tubes (Shalaby et al. 2014) and centrifuged using (Centurion, Scientific Ltd., USA) at $373 \times g$ for 20 min. Sera were collected and stored at -80°C for further biochemical analysis. Moreover, liver and visceral fats were excised, cleaned, weighted, and recorded for each group. Liver adipose tissues were homogenized and stored in -80°C for western blotting of PPAR- γ and AMPK-1 α expression, and for PCR analysis of gene expression for free fatty acids (FFAs) and sterol regulatory element-binding protein 1 (SREBP-1C) expression. Moreover, the liver adipose tissues were collected in 10% formalin for histopathological investigations. In this experiment, rats were randomly assigned according to a randomization table (Shalaby et al. 2014). A technical assistant performed animals' allocation and drug treatment in a blinded manner. All biochemical and histopathological examinations were assessed by investigators blinded to the experimental groups.

Biochemical Parameters

The following parameters were assessed in animal sera colorimetrically using their corresponding kits. Alanine transaminase (ALT) and aspartate transaminase (AST) (BioMed-GPT, and BioMed-GOT, Cairo, Egypt, respectively). Total cholesterol (TC), triacylglycerides (TG), high-density lipoprotein (HDL) by Spectrum Egyptian Co. for Biotechnology, Cairo, Egypt. Low-density lipoprotein (LDL) (Stanbio laboratory, Boerne, TX, USA), fasting blood glucose (FBG) (BioMed-glucose L.S, Egy-chem, Cairo, Egypt), malondialdehyde (MDA) and glutathione (GSH) (Biodiagnostic, Giza, Egypt).

Chromatographic Analysis

The analysis was performed using Waters Corp. (USA) delivery system accessorized with an ACQUITY H-Class-Xevo TQD triple-quadrupole tandem mass spectrometer with an electrospray ionization (ESI) interface. Methanol was used to dissolve the samples (Sigma Aldrich, Germany), in a concentration of 1 mg/ml, followed by filtration using a micropore filter of 0.2- μm pore size. The mobile phase composition was 0.01% formic acid in purified water (A), and acetonitrile (B) with the following elution gradient: 0–4 min, 15% B; 4–5 min, 20% B; 5–10 min, 30% B; 10–11 min, 45% B; 11–33 min, 55% B; 33–35 min, 70% B; 35–40 min, 90% B; 40–45 min, 15% B. The injection volume was 10 μl and the flow rate was 1 ml/min. At mass ranges (100–1000 m/z), the analytes were observed. MS scans were performed at 3.5 kV

capillary voltage, 20–95 V cone voltage detection, 2.5 V radio frequency (RF) lens voltage, 150°C source temperature, and 500°C desolvation gas temperature. At flow rates of 1000 and 20 l/h, nitrogen was used as a desolvation and cone gas, respectively. Mass Lynx 4.1 software was used to monitor system operation and data collection (Elshamy et al. 2021).

Antioxidant Assay

The antioxidant effects of the different samples were measured using 2,2-diphenyl-1-picrylhydrazyl (DPPH $^\bullet$) radical scavenging assay, according to (Scapin et al. 2016), and the cupric ion reducing activity (CUPRAC) was determined according to method described by Apak et al. (2006).

Enzyme Link Immunosorbent Assay

Commercial ELISA kits were used, according to the manufacturer's instructions, to measure serum insulin (Cusabio, Wuhan, China) and liver homogenate leukotriene LT-B4, leptin, and adiponectin (MyBioSource, San Diego, USA, Cusabio, Kampenhout, Belgium and RayBiotech, Inc., Norcross, GA, USA). Results were expressed as picogram/milligram of protein.

Quantitative Real-time PCR

The expressions of FFAs and SREBP-1C genes were determined using RT-PCR. Total RNA was extracted from liver tissues using RNeasy RNA extraction Kit (Qiagen, MD, USA). First, the purity of extracted RNA was verified using spectrophotometry (dual-wavelength Beckman, Spectrophotometer, USA) by recording the optical density (OD) at 260/280 nm. Second, equal amounts of extracted RNA were reverse-transcribed using RT-PCR kit (Fermentas, Waltham, USA). Third, quantitative RT-PCR was carried out using SYBR Green. The sequences of primers used in the present investigation are presented in Table S1.

Western Blot Analysis

Liver tissue levels of PPAR- γ and AMPK-1 α were analyzed using the western blot methodology. Liver homogenate was prepared in RIPA buffer and centrifuged, and protein concentration was determined using Bradford Protein Assay Kit (Bio Basic Inc., Markham, Canada) for quantitative protein analysis. Equal amounts of protein solutions were separated using SDS-PAGE (10% acrylamide gel) (Bio-Rad Laboratories, California, USA). The separated proteins were transferred onto polyvinylidene difluoride (PVDF) membranes and blocked with tris-buffered saline and tween 20 (TBST) buffer and 3% bovine serum albumin (BSA) for 1 h at room temp. Next, the membranes were incubated overnight at 4°C with the primary antibodies against PPAR- γ and AMPK-1 α

(Thermo Fisher Scientific, MA, USA). After washing with TBST three times, membranes were incubated with horseradish peroxidase (HRP)-conjugated goat anti-rabbit- IgG (Novus Biologicals, CO, USA) for 1 h at room temperature. Finally, the band intensity was visualized using a Chemi-Doc™ imaging system (Clarity™ Western ECL substrate, Bio-Rad, CA, USA) with Image Lab™ software version 5.1 (Bio-Rad Laboratories, Inc., Hercules, CA, USA).

Histopathological Examination

Liver tissue samples were collected and fixed in 10% buffered formalin for 24 h. Afterwards, they were processed and embedded in paraffin wax sections for further histopathological investigation using hematoxylin and eosin (H&E) stain (Sigma Aldrich St. Louis, MO, USA) (Bancroft and Gamble 1996).

Statistical Analysis

GraphPad Prism software, version 5.01, was used for the statistical analysis of the groups. Results were presented as mean $\pm$ SD (standard deviation) and assessed using the one-way analysis of variance (ANOVA) procedure followed by Tukey's multiple range test. A *p* value less than 0.05 was considered statistically significant, where ^a*p* < 0.001, ^b*p* < 0.01, and ^c*p* < 0.05; ns = statistically not significant.

Results and Discussion

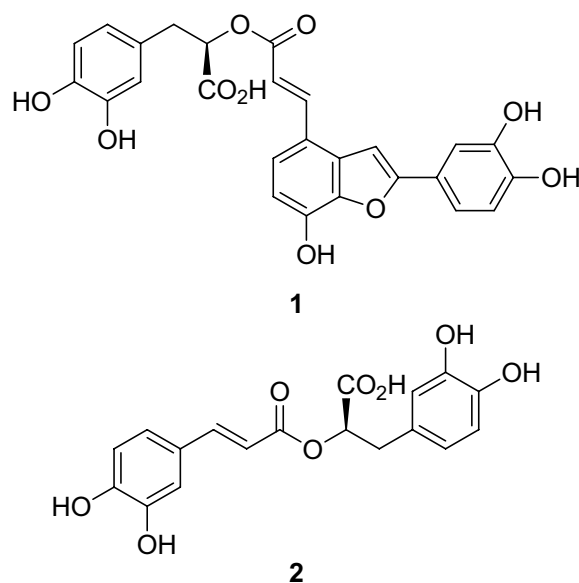
Total Phenolic and Flavonoid Contents

The total polyphenol and total flavonoid contents observed in quinoa were 28.2 mg gallic acid equivalent (GAE)/g and 247 mg quercetin equivalents (QE)/g; in chia were 53.2 mg gallic acid equivalent (GAE)/g and mg quercetin equivalents (QE)/g, respectively.

Dereplication of Bioactive Metabolites

The constituents in the bioactive extracts were detected using the HPLC/PDA/ESI/MS method, as presented in Tables S1 and S2. The peaks were interpreted by comparison with reported data for the fragmentation pattern of the deprotonated ion $[M - H]^-$ (Table S2 and S3). Figure S2 illustrates the chromatograms obtained from both the chia (Fig. S2A) and quinoa (Fig. S2B), where the following major antioxidants components were dereplicated and should be mentioned: salvianolic acid C (1; Rt 12.75 min; 13.8%) from

chia seeds, and rosmarinic acid (2; Rt 12.72 min; 14.9%) from quinoa seeds.



Antioxidant Effects

DPPH results of quinoa showed 100.40% compared to vitamin C. As for chia, 90.94% was observed. CUPRAC assay of the seeds showed 934.77 μ g/ml and 1109.75 μ g/ml BHA concentration for quinoa and chia, respectively.

Weight Management Effect

Body weight of the quinoa group showed no significant change recorded in weeks 1–3, while a significant decrease in weeks 4–6 in comparison to weeks 1 and 2 was observed (Fig. S3). Furthermore, significant decrease in weeks 5 and 6 was reported in comparison to the first 4 weeks. As for chia group, results showed no significant change in body weight of the rats in weeks 1–3, while a significant decrease in body weight of the rats in week 4 in comparison to the first week was observed. Moreover, a significant decrease in body weight in weeks 5 and 6 was seen in comparison to the first 4 weeks. No significant change in body weight of the rats appeared in weeks 1–3 (*p* > 0.05).

Protection of Liver Enzymes

Rats fed HFD showed more than 2.5-fold increase in ALT and AST levels compared to the negative control group (Group I). Treatment with hydroalcoholic extracts showed significant reduction in liver enzymes ALT and AST by 55.6% and 50.6%

for quinoa 62.5% and 58.5% for chia seeds, respectively, as compared to untreated obese rats. No significant difference was observed between the chia, quinoa, and green treated groups (Fig. 1A and B).

Lipid Profile Improvement

As depicted in Fig. 1C–F, rats on HFD (Group II) showed significant 91%, onefold and threefold increases in total cholesterol (TC), triacylglycerides (TG), and low-density lipoprotein (LDL) levels, while high-density lipoprotein (HDL) levels were reduced by 54.7% as compared to rats on normal chow diet (Group I), respectively. Treatment with the seeds' hydroalcoholic extracts improved the lipid profile of rats on HFD compared to the non-treated group, manifested by reduction in TC, TG, and LDL and elevation in HDL levels by 32.5, 43.25, 46, and 64.38% for quinoa and by 33, 30.25, 48.75, and 74.25% for chia extract. Compared to the reference group that received green tea as treatment (Group III), quinoa group showed reduction in TG levels by 25.5%. No significant difference between quinoa (Group IV) and chia extracts (Group V) was detected.

Glycemic Profile Improvement

Rats on HFD showed significant increase in fasting blood glucose (FBG) and serum insulin levels by more than 2.5-fold and 1.3-fold, as compared to the negative control group (Group I). Treatment with quinoa showed ample reduction in FBG and insulin levels by 43.8%. As for chia, reductions of 52.3 and 56.9% have been observed as compared to untreated obese rats, respectively. No significant change in glycemic profiles of green tea (Group III), quinoa (Group IV), and chia (Group V) treated groups was noticed (Fig. 1G and H).

Anti-inflammatory Effect

As illustrated in Fig. 2A, leukotriene LT-B4 levels showed a significant increase in HFD group (Group II) in comparison to rats on normal diet by 225.81%. LT-B4 levels in quinoa and chia groups showed significant decrease in comparison to HFD group by 49.4% and 45.21%, respectively. No significant change between the reference group (HFD + green tea) and the treatment groups was observed. Moreover, both seeds showed the same extent of anti-inflammatory effect.

Leptin and Adiponectin Modulation

According to Fig. 2B and C, leptin levels were elevated, and adiponectin levels were reduced in HFD group (Group II) obese rats compared to rats on normal diet by 3.6-fold and 74%, respectively. Treatment with the seed extracts reduced

leptin levels by 67.2% (quinoa) and 54.26% (chia). On the other hand, adiponectin levels were increased by 1.3-fold and 1.9-fold for quinoa and chia extracts, respectively. No significant change between reference group (HFD + green tea) and treated groups was observed. Noteworthy, quinoa restored leptin levels to normal values of NFD group (Group I). Moreover, both seeds showed the same modulatory effects on leptin and adiponectin levels.

Oxidative Stress Markers

Rats fed with HFD (Group II) showed a significant raise in malondialdehyde (MDA) levels by threefold and reduced glutathione (GSH) levels by 61%, compared to rats on normal diet (Group I). Treatment with the seeds' extracts reduced MDA levels by 44.5% and 67.3% for the quinoa group and by 37.24% and 62.8% for the chia group, as compared to obese rats treated with green tea (Group III) and the non-treated one (Group II), respectively. The antioxidant marker GSH has been enhanced by onefold following treatment of obese rats with both extracts as compared to the non-treated group. Moreover, GSH levels demonstrated no significant difference between the three herbal groups. Furthermore, no significant difference has been reported between chia and quinoa groups, as compared to the GSH levels in the negative control group (Group I), as shown in Fig. 2D and E.

PPAR- γ and AMPK-1 α Levels

As illustrated in Fig. 3A and B, PPAR- γ and AMPK-1 α were reduced in obese rats compared to rats on normal diet by 85.37 and 79%, respectively. Treatment with the seeds reversed this reduction by fourfold for quinoa's and chia's PPAR- γ levels and by 1.9-fold for quinoa's and twofold for chia's AMPK-1 α levels. Compared to the reference group (HFD + green tea), quinoa and chia extracts increased the PPAR- γ levels by 26.24 and 31.27%, respectively. AMPK-1 α levels showed no significant change between the reference group (HFD + green tea) and the treatment groups. Moreover, both seeds showed the same modulatory effects on PPAR- γ and AMPK-1 α protein levels.

FFA and SREBP Levels

As depicted in Fig. 3C and D, gene expressions of FFA and SREBP-1c were elevated in obese rats compared to rats on normal diet by sevenfold and 4.7-fold, respectively. Treatment with the seeds curbed the elevation by 65% for quinoa's and 58% for chia's FFA levels and by 58.6% for quinoa's and 44.4% for chia's SREBP-1 expression levels. It is worth mentioning that the quinoa group showed a greater extent of reduction in FFA expression levels, as compared

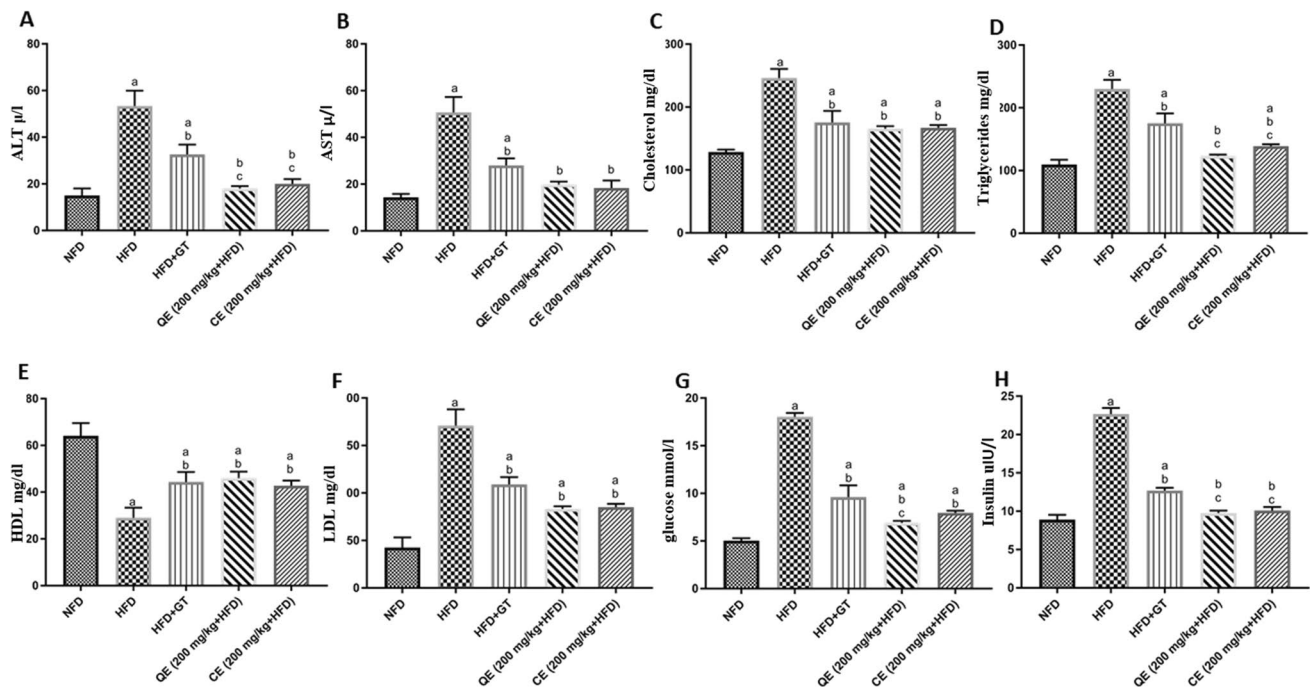


Fig. 1 Effect of quinoa and chia seeds' hydroalcoholic extracts on serum: **A** ALT levels, **B** AST levels, **C** cholesterol levels, **D** triacylglyceride levels, **E** HDL levels, **F** LDL levels, **G** fasting blood glucose levels, **H** insulin levels. Data are expressed as mean ± SD of three

independent experiments ($n=6$). Significant differences were identified as follows: ^asignificantly different from the control group (normal food diet); ^bsignificantly different from the high-fat diet group; ^csignificantly different from the reference group at $p < 0.05$

to the reference group (HFD + green tea) by 29%. SREBP-1 expression levels showed no significant change between the reference group (HFD + green tea) and the treatment groups. Moreover, both seeds showed the same modulatory effects on FFA and SREBP-1 expression levels.

Histopathological Alteration

Liver of rats on HFD revealed histopathological alterations where fibroblastic cell proliferation with inflammatory cells infiltration surrounding the bile duct associated with congestion in the portal vein was demonstrated. Treatment with quinoa showed normal liver architecture similar to the control group with no histopathological alterations. Notably, the protective effect of quinoa on a high-fat diet seemed to exceed the reference and the chia groups, where rats on HFD treated with green tea showed dilatation in the central vein and sinusoids, while the parenchyma showed ballooning degeneration in the hepatocytes with congestion in the sinusoids in between. The chia-treated group showed mild congestion in the central vein, as shown in Fig. 4A–E.

Obesity is considered a global pandemic ascribed to a combination of genetic susceptibility, increased availability of fast foods, and decreased requirement for physical activity in urban life. It should no longer be recognized as simply as a cosmetic challenge for certain individuals, but an epidemic that

threatens global health. To date only few approved common therapies are available due to reported limitations, possible tolerance, and unfavorable side effects as diarrhea and abdominal cramps. Thus, an effective safe natural alternative is a pressing need nowadays (Payab et al. 2020; Aron-Wisnewsky et al. 2021). The present study addressed the potential anti-obesity role of commonly prescribed seeds by practitioner for effective diet and better lifestyle: quinoa and chia seeds. This investigation was done via evaluating the PPAR- γ /AMPK-1 α signalling pathway and the key-players parameters affecting adipogenesis and lipogenesis in high-fat diet-induced rat model. In correlation with the metabolic complications associated with obesity. Where inflammation and oxidative stress are the main activators in this pathway affecting lipid and glycemic profiles along with liver malfunction. Endowed with their antioxidant, anti-inflammatory, and insulin-sensitizing activities, results of the current work corroborate evidence-based reports to the use of quinoa and chia seeds in weight management. Furthermore, green tea has been chosen as a reference drug as it is reported to be one of the most efficient anti-obesity nutraceuticals. Green tea was proved to have an antioxidant effect through increasing the endogenous antioxidants and decreasing the oxidative stress markers (Zhu et al. 2019). Also, it was found to have a potent anti-inflammatory activity via decreasing the circulating inflammatory cytokines and enhancing the adipokine hormones (Bagheri et al. 2020). Moreover, it was previously

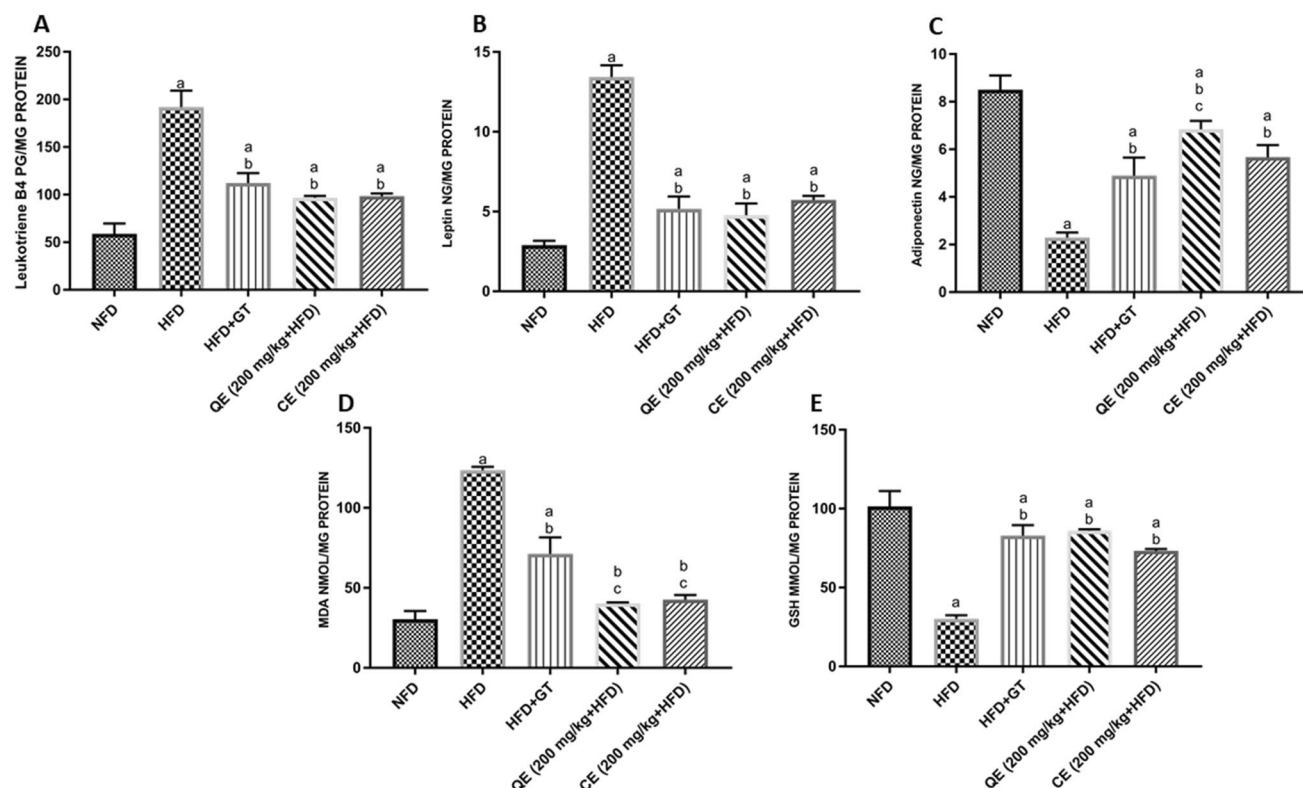


Fig. 2 Effect of quinoa and chia seeds' hydroalcoholic extracts on serum: **A** LT-B4 levels, **B** leptin levels, **C** adiponectin levels, **D** MDA levels, **E** GSH levels. Data are expressed as mean $\pm$ SD of three independent experiments ($n=6$). Significant differences were identi-

fied as follows: ^asignificantly different from the control (NFD) group; ^bsignificantly different from the (HFD) group; ^csignificantly different from the reference (HFD + green tea) group at $p < 0.05$

reported that green tea enhanced lipid and glycemic profile in test subjects (Asbaghi et al. 2020). Green tea was also reported to exert its anti-obesity activity through the upregulation of PPAR- γ /AMPK-1 α signalling pathway (Jiang et al. 2020).

Noteworthy, it has been reported that some obesity-related complications such as inflammation along with oxidative stress, hyperlipidemia, and insulin insensitivity are unequivocal risk factors of metabolic syndrome (Eckel et al. 2005), with higher chances for cardiovascular, hyperlipidemia, type 2 diabetes mellitus, and psychiatric comorbidities (Aballay et al. 2013). Such findings are consistent with results of the present investigation, where rats on HFD showed distorted lipid, glycemic, and adipokine profiles, along with inflammation and oxidative stress. On the other hand, animals treated with both seeds' extracts effectively reduced body weight compared to the non-treated group. Both extracts amended the lipid, glycemic, oxidative stress, and adipokine profiles of obese rats. They mitigated elevated serum TG and TC content, decreased LDL, and increased HDL levels. Moreover, the extracts were able to enhance GSH and reduce MDA levels; all treatment groups showed a decrease level of insulin and glucose compared to the HFD group. Therefore, our results are consistent with previous

research, which stated that the test seeds could modulate lipid profile (Munir et al. 2021; Yao et al. 2021; Oliva et al. 2021).

Notably, obesity results in an altered adipokine profile, with upregulated expression of pro-inflammatory cytokines and leptin, and reduced levels of anti-inflammatory adipokines, such as adiponectin (Hotamisligil 2017). Our outcomes confirmed the ability of the extracts to decrease the level of LT-B4 and leptin, with concurrent increase in adiponectin in test subjects. PPAR- γ , a ligand-dependent transcription factor highly expressed in adipocytes, plays an important role in adipogenesis, lipid storage (Antonopoulos et al. 2016), and insulin sensitivity. Noteworthy, oxidative stress and inflammation are directly linked to PPAR- γ pathway where inflammatory cytokines resulting from increased reactive oxygen species downregulate the expression of PPAR- γ (Algendaby 2020). Our results demonstrated that the seed extracts displayed antioxidant potential by reducing MDA and enhancing GSH, and hence ameliorating obesity by modulating PPAR- γ transcriptional effect and activating the phosphorylation of AMPK-1 α . This process is essential for suppression of proteolytic processing, fatty acid oxidation, and transcriptional activity of SREBP-1c which inhibits adipogenesis via promoting lipolysis in adipose tissue and

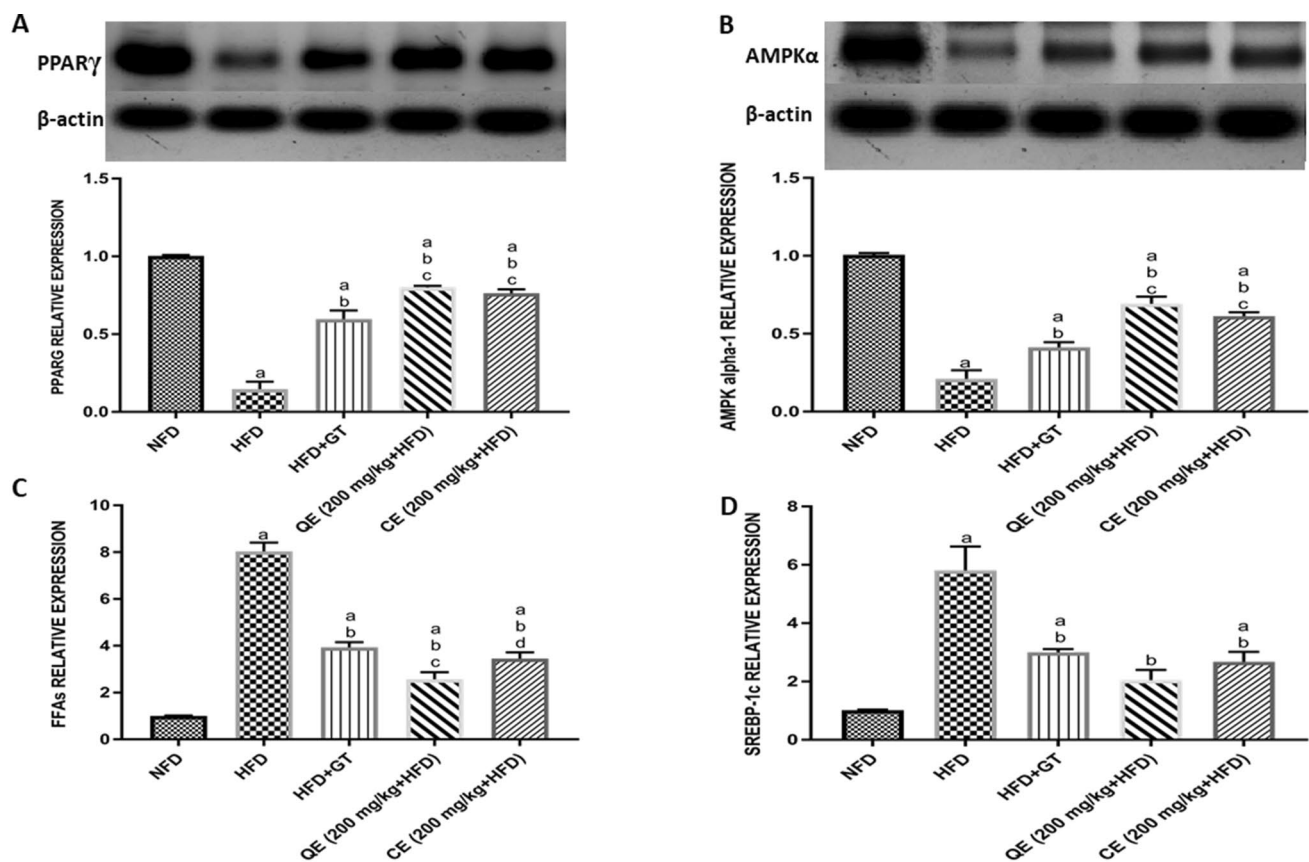


Fig. 3 Effect of quinoa and chia seeds' hydroalcoholic extracts on serum: **A** PPAR- γ , **B** AMPK-1 levels, **C** FFA levels, **D** SERBP levels. Data are expressed as mean $\pm$ SD of three independent experiments ($n=6$). Significant differences were identified as follows:

^asignificantly different from the control (NFD) group, ^bsignificantly different from the (HFD) group, ^csignificantly different from the reference (HFD + green tea) group, ^dsignificantly different from the quinoa group at $p < 0.05$

stimulating fatty acid oxidation in the liver (Ho et al. 2019). In addition to its regulation of insulin function, they also regulate the expression of genes controlling free fatty acids, cholesterol, and synthesis of lipids (Damiano et al. 2019). The results here show a clear upregulation of PPAR- γ signalling pathway, which in turn lead to reduction in FFA's and SREBP-1c levels.

These findings could be further elaborated by the presence of the rich phenolic profile of both seeds. Quinoa seeds are rich in quercetin malonyl-hexoside (5.2%) and kaempferol dirhamnoside (9.21%) which were reported to display antioxidant and anti-inflammatory effects (Cheng et al. 2014; Dabeek and Marra 2019; Kadhum and Thuwaini 2021). On the second hand, these phenolics inhibit lipogenesis and promote lipolysis which in turn suppress lipid accumulation through modulating PPAR- γ /AMPK- α signalling pathway (Khelifi et al. 2020). Furthermore, the presence of dihydroxybenzoic acid-pentoside (7.88%) is reported to have synergetic anti-inflammatory and antioxidant effects (Quaresma et al. 2020), as well as modulating glucose and lipid metabolism (Xochitl et al. 2021). The

anti-obesity activity could also be related to the presence of hydroxycinnamic acid (4.95%) and its derivatives including caffeic and ferulic acid hexoside (2.01 and 7.9%, respectively) which were reported to improve lipid metabolism, modulate adipokine hormones (Agregán et al. 2021), and exert antioxidant effect through inhibiting lipid peroxidation and radical scavenging activity (Yuan et al. 2022). Moreover, decreased lipid accumulation and improvement of serum lipid profile could be accredited to the presence of apigenin pentosyl (7.2%) which was reported to inhibit the accumulation of lipids (Bai et al. 2017). Hydroalcoholic extract of quinoa seed was found to be enriched with rosmarinic acid (14.95%) and its derivatives, which were reported to possess lipid lowering effect by decreasing serum total cholesterol and triacylglycerides besides modulating lipid profile. Additionally, it was found to inhibit α -glucosidase which in turn inhibits lipid accumulation (Zhou et al. 2021). Also, rosmarinic acid upregulates PPAR- γ levels, and henceforth decreasing adipogenesis in coordination with decreasing inflammation by modulating adipokine hormones (Vasileva et al. 2021).

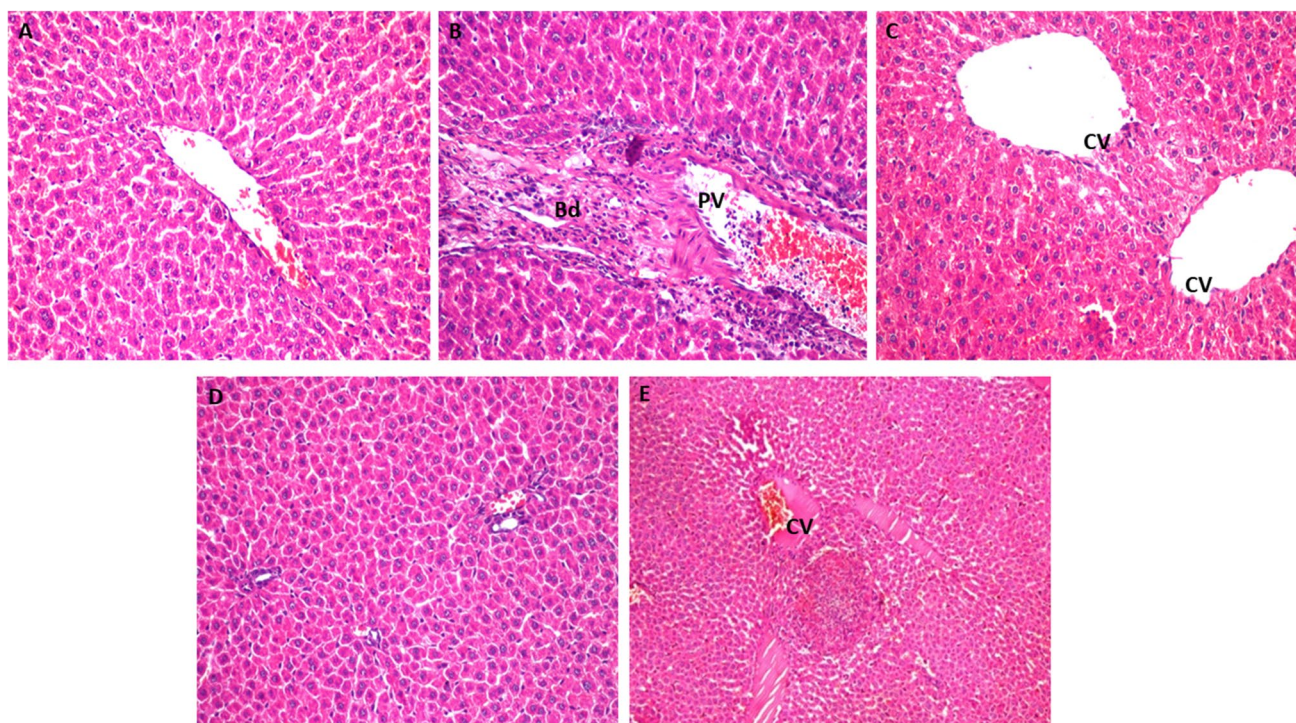


Fig. 4 Representative photomicrograph of the liver tissue sections in each experimental group (H&E, ×40): **A** control (NFD) group, **B** (HFD) group, **C** (HFD + green tea) group, **D** (HFD + quinoa) group, **E** (HFD + chia) group. Bd, bile duct; PV, portal vein; CV, central vein

Chia seeds showed a high content of salvianolic acid C (13.8%), as the major dereplicated antioxidant, which showed a potent α -glucosidase inhibitory activity with IC_{50} of $3.03 \pm 0.27 \mu M$ (Tang et al. 2019). Also, this polyphenol inhibited LPS-induced inflammatory response and NF- κB activation through the activation of AMPK/Nrf2 signaling both *in vivo* and *in vitro* (Song et al. 2018). In addition, a high content of malic acid was found (7.49%), which is reported to be a potent lipase inhibitor, where it decreases the fat absorption in the intestine which in turn improves the lipid profile (Porrás-Mija et al. 2020). Moreover, the presence of syringic acid and caffeic acid and their glycosides (3.89, 2.01%, respectively) contribute to slim-aid effect of chia due to inhibitory effect on α -amylase and lipase enzymes, which modulate adipogenesis and lipogenesis process in the body (Hegazi et al. 2020). Owing to the presence of danshensu glucuronide (13.83%) which suppresses ROS formation, decreases lipid peroxidation, and promotes anti-inflammatory effects (Nicolì et al. 2019) and act as an PPAR- γ agonist, hence upregulates PPAR- γ /AMPK- α signalling pathway leading to modulation of adipogenesis along with decreasing insulin resistance and improving glycemic profile (Xu et al. 2017).

Morbid obesity enhances accumulation of fats on liver, which eventually leads to liver fibrosis and histopathological complications (Xiong et al. 2017). Our hepatic histopathological findings of obese rats showed drastic damage

in the portal vein and hepatocytes rupture with high severity along with elevated liver enzymes in comparison to seed extracts-treated groups. This goes in harmony with previous studies which showed the hepatoprotective effect of quinoa (Saxena et al. 2017) and chia seeds (Apoorva et al. 2020). The presence of salvianolic acid C (13.79%) and ferulic acid hexoside (7.9%) in the quinoa-treated group could be a reason behind its hepatoprotective effects, in line with Wu et al. (2019) and Peng et al. (2021). As for chia seeds, the presence of caffeic acid derivative (22.59%), rosmarinic acid (14.95%), and malic acid (7.49%) could be the reason behind the observed hepatoprotective profile as previously described (Kaur et al. 2019; Hiraishi et al. 2022).

Conclusion

The present study evidenced that supplementation with quinoa and chia reduced body weight gain, contributed to control blood glycemic profile, and decreased the atherogenic index of plasma. Both seeds' supplementation reduced adipogenesis through the downregulation of adipogenesis transcription factors and lipogenesis mediators, in addition to their upregulatory effect of oxidative-encoding genes and downregulatory effect of lipogenic-related genes. Results hypothesized the potential applicability of the test seeds components in the prevention of obesity and its related

disorder, introducing to medical community and food industry an economic and alternative safe approach to halt metabolic syndrome comorbidities.

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Author Contribution NHO: investigation, formal analysis, methodology, manuscript writing, and proofreading. AAZE-B: formal analysis, methodology, manuscript writing, and proofreading. HTAH: formal analysis. HH: setting the protocol, practical supervision, formal analysis, methodology, manuscript writing, and proofreading.

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Data Availability The data to support the findings of this study are included within the article or in the supplementary data.

Declarations

Ethical Approval Experimental procedures were conducted in accordance with the Egyptian National Institutional Guidelines on Animal Experimentation and approved by the Animals Ethics Committee at the GUC (#PB35879) obtained 28.6.2020 in association with the recommendations of the National Institutes of Health (NIH) Guide for Care and Use of Laboratory Animals (Publication No. 85–23, revised 1985).

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