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Quinoa ameliorates renal endoplasmic reticulum stress in Glucocorticoid-induced insulin resistant rats

La quinua mejora el estrés del retículo endoplásmico renal en ratas con resistencia a la insulina inducida por glucocorticoides.

Ahmet Cihat Öner [1]*, ***Ayşe Usta*** [2]

[1] *Van Yuzuncu Yıl University, Faculty of Veterinary Medicine, Department of Pharmacology and Toxicology, TR-65080 Van-Türkiye*
[2] *Van Yuzuncu Yıl University, Faculty of Science, Department of Chemistry, TR-65080 Van-Türkiye*
* *Corresponding author: ahmetcihatoner@yyu.edu.tr*

ABSTRACT

The objective of this study was to investigate the efficacy of quinoa (*Chenopodium quinoa*) on endoplasmic reticulum stress responses in the kidneys of rats with dexamethasone-induced insulin resistance. In this study, 42 male rats were selected as the subjects for the investigation. These rats were randomly allocated to six groups: a healthy control group, a control group fed with quinoa, an IR group, and three treatment groups that received metformin, quinoa, or quinoa prior to the induction of insulin resistance. Subsequently, the values of fasting glucose, serum insulin, and Homeostatic Model Assessment of Insulin Resistance were recorded. An additional six endoplasmic reticulum stress-related genes (Xbp1, Perk, Ire1, Chop, Atf6, and Atf4) were then quantified. The investigation revealed the presence of rats exhibiting extreme metabolic dysfunction under dexamethasone, and a significant elevation in Homeostatic Model Assessment of Insulin Resistance was observed in the insulin resistance group (7.11 ± 1.12) compared to the control group (2.88 ± 0.13). This metabolic stress was, in turn, correlated with the renal endoplasmic reticulum stress pathway, with all six genes significantly upregulated (Chop: 4.12-fold, and Perk: 5.916-fold). The addition of quinoa resulted in a significant reduction in metabolic molecular dysfunctions. In the insulin resistance + Quinoa group, the Homeostatic Model Assessment of Insulin Resistance was found to be significantly lower (6.33 ± 1.04, $P < 0.05$), and the pro-apoptotic Chop gene expression in this group of rats was found to be significantly decreased by 59 % (from 4.12-fold to 1.79-fold). The effect of quinoa on Homeostatic Model Assessment of Insulin Resistance and endoplasmic reticulum stress gene expression is comparable to that of metformin. This suggests that the consumption of quinoa may help to counteract the molecular alterations and metabolic disturbances associated with the endoplasmic reticulum stress caused by glucocorticoid-induced insulin resistance. Consequently, quinoa could be a useful dietary addition in cases of insulin resistance-related renal complications.

Key words: Chenopodium quinoa; endoplasmic reticulum stress genes; glucocorticoid; insulin resistance; kidney.

RESUMEN

El objetivo del estudio fue investigar la eficacia de la quinua (*Chenopodium quinoa*) para atenuar las respuestas del retículo endoplásmico al estrés en los riñones de ratas con resistencia a la insulina inducida por dexametasona. Para la investigación se seleccionaron 42 ratas macho. Las ratas se dividieron aleatoriamente en seis grupos: un grupo de control sano, un grupo de control alimentado con quinua, un grupo con RI y tres grupos de tratamiento que recibieron metformina, quinua o quinua antes de inducir la resistencia a la insulina. Posteriormente, se registraron los valores de glucosa en ayunas, insulina sérica y la evaluación del modelo homeostático de la resistencia a la insulina. A continuación, se cuantificaron seis genes relacionados con el estrés del retículo endoplásmico (Xbp1, Perk, Ire1, Chop, Atf6 y Atf4). El estudio reveló que algunas ratas presentaban una disfunción metabólica extrema bajo dexametasona y se observó un aumento significativo de la evaluación del modelo homeostático de la resistencia a la insulina (7,11 ± 1,12) en el grupo con resistencia a la insulina en comparación con el grupo de control (2,88 ± 0,13). Este estrés metabólico se correlacionó con la vía del estrés del retículo endoplásmico renal, lo que dio lugar a una regulación al alza significativa de los seis genes (Chop: 4,12 veces y Perk: 5,916 veces). La adición de quinoa dio lugar a una reducción significativa de las disfunciones moleculares metabólicas. En el grupo resistencia a la insulina + Quinoa, la evaluación del modelo homeostático de la resistencia a la insulina era significativamente más bajo (6,33 ± 1,04; $P < 0,05$) y la expresión del gen proapoptótico Chop se redujo significativamente en un 59 % (de 4,12 a 1,79 veces). El efecto de la quinoa sobre la evaluación del modelo homeostático de la resistencia a la insulinay la expresión génica del estrés del retículo endoplásmico es comparable al de la metformina. Esto sugiere que el consumo de quinoa puede ayudar a contrarrestar las alteraciones moleculares y los trastornos metabólicos asociados al estrés del retículo endoplásmico causado por la resistencia a la insulina inducida por glucocorticoides. Por tanto, la quinua podría ser un complemento dietético útil en casos de complicaciones renales relacionadas con la resistencia a la insulina.

Palabras clave: Chenopodium quinoa, genes del estrés del retículo endoplásmico, glucocorticoides, resistencia a la insulina, riñón.

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INTRODUCTION

Insulin resistance (IR) is a metabolic disorder that arises from a decrease in the sensitivity of peripheral organs such as muscle, liver, and adipose tissue to insulin. This results in impaired glucose regulation over time. As this process progresses, blood sugar levels may remain consistently elevated, thereby accelerating the development of type II diabetes. It is evident that IR is associated with metabolic comorbidities, including but not limited to hypertension, dyslipidaemia, and obesity. These conditions have been demonstrated to contribute to renal dysfunction and elevate the risk of chronic kidney disease [1].

Glucocorticoids, dexamethasone (DEX) in particular, provide a trustworthy approach to researching the pathogenesis of IR in metabolic syndrome [2]. Although it is known that DEX strongly evokes IR by inhibiting insulin signaling pathways in the liver and muscles shortly after administration, it is also known that it induces measurable stress responses in highly active metabolism-bearing organs such as the kidneys [3]. Focusing on these points, it appears that Endoplasmic Reticulum (ER) stress is an important factor in establishing the relationship between glucocorticoid-induced IR and kidney injury [4].

Based on the IR model induced by DEX administration, it is clearly acknowledged that not only the similarities in metabolic disorders in IR can be reproduced in humans, but even the activation of Unfolded Protein Response pathways leading to ER Stress in kidneys is simulated in renal tissues. The strategic use of this model allows for a detailed investigation into how potential therapeutic agents, such as quinoa, simultaneously modulate both systemic IR and specific cellular stress mechanisms endoplasmic reticulum stress (ER stress) at the renal level [5]. Consequently, this study aims to elucidate the protective effects of quinoa on renal ER stress using the DEX-induced IR model, providing insights at the molecular level.

Moreover, the fact that quinoa contains a wide range of bioactive compounds and has established antioxidant and anti-inflammatory properties suggests a strong potential for using quinoa in relation to cellular stress responses, such as ER stress, which is mostly exacerbated by oxidative damage and inflammation. The ER is an crucial cellular organelle, playing critical role in the protein synthesis, folding, and the regulation of calcium within the cell. In the scenario where the folding of proteins in the ER becomes overwhelmed, the cell responds to the stress using a unique response called the unfolded protein response (UPR). Although this response aims to restore cellular balance, its prolonged duration can cause damage in many organs, including kidney tissue [6 , 7].

In kidneys, ER stress has been implicated in diabetic nephropathy and acute renal failure, which are generally marked by an increase in major stress genes, including Xbp-1, Atf4, Chop, Perk, Ire-1, and Atf6. The continuous activation of these genes ultimately leads to cellular apoptosis and fibrosis in the kidneys [8 , 9 , 10]. Therefore, targeting ER stress may present a viable therapeutic strategy for IR-induced renal dysfunction [11].

However, despite the rising interest in the metabolic response of quinoa, its exact role in ER stress, especially in the kidneys of glucocorticoid-induced insulin-resistant animals, has never been well explored. Hence, the principal aim of our study was to evaluate the potency of quinoa treatment in blunting both the metabolic disturbances Model Assessment of Insulin Resistance (HOMA-IR) and the molecular indices of ER stress (Xbp1, Chop, and so on) in the kidneys of DEX-induced insulin-resistant rats. We hypothesized that quinoa would exert a substantial protective effect, like the concurrent standard of care metformin, by downregulating the fundamental ER stress-responsive gene expression.

MATERIAL AND METHODS

Animals

Forty-two adult male Wistar albino rats (*Rattus norvegicus*), weighing 200–250 g, were obtained from the Van Yuzuncu Yil University Experimental Application and Research Centre. The animals were housed in standard polycarbonate cages under controlled environmental conditions, including a 12-hour (h) light/dark cycle, a constant temperature of 22 ± 2 °C, and a relative humidity of 55 ± 5 %.

All rats had *ad libitum* access to standard chow and fresh water. The kidney tissues used in this study were permitted from Van Yüzüncü Yıl University Animal Experiments Local Ethics Committee (YUHAD-YEK, date: 31/11/2019; decision number: 2019/10).

Experimental design and groups

After a one-week acclimatization period, the rats were randomly allocated into six experimental groups (n = 7 per group). The experiment was conducted over a total of 13 days (d).

- **Control Group (C):** Received standard chow and daily intraperitoneal (i.p.) injections of physiological saline for 13 d.
- **Quinoa Group (Q):** Fed a quinoa-supplemented diet for 6 d, followed by standard chow and saline injections for the subsequent 7 d.
- **Insulin Resistance Group (IR):** Fed standard chow for 13 d and received i.p. injections of dexamethasone (DEX; 1 mg/kg/day) for the final 7 d to induce insulin resistance.
- **IR + Metformin Group (IM):** Insulin resistance was induced with DEX (1 mg/kg/day, i.p.) for 7 d, followed by a 6-d treatment period with metformin (40 mg/kg/d, oral gavage) while being fed standard chow.
- **IR + Quinoa Group (IQ):** Insulin resistance was induced with DEX (1 mg/kg/d, i.p.) for 7 d, followed by a 6-d treatment period with the quinoa-supplemented diet.
- **Quinoa + IR Group (QI):** Fed the quinoa-supplemented diet for 6 d (prophylactic treatment), followed by 7d of DEX injections (1 mg/kg/d, i.p.) to induce IR.

Diet preparation and treatments

The standard chow diet consisted of 23 % crude protein, 2.7 % crude fat, 6.5 % crude cellulose, and 7.8 % crude ash (Bayramoğlu Feed and Flour Industry, Erzurum, Türkiye). The quinoa-supplemented diet was prepared by mixing finely ground

quinoa seeds (*Chenopodium quinoa*) and ground standard chow in a 1:1 ratio by weight. This mixture was formed into pellets using a feed pellet machine and air-dried. The diets were formulated to be approximately isocaloric. DEX was dissolved in physiological saline for injections. Metformin was dissolved in distilled water for oral gavage.

Biochemical analysis

Serum insulin concentrations were quantified using an enzyme-linked immunosorbent assay specifically designed for rats (FineTest, Rat INSELISA, ER1113). The HOMA-IR was used to evaluate IR. For this purpose, fasting glucose measurements were obtained from tail-vein blood samples collected two h after the final experimental intervention.

The HOMA-IR index was computed according to the commonly used formula described by Salari *et al*. [12]:

HOMA-IR = fasting plasma glucose (mg/dl) × fasting plasma insulin (µm/l) / 405

Sample collection

At the completion of the study on d 13, the animals were anesthetized, and blood samples were obtained by performing a cardiac puncture. The collected blood was centrifuged at 12000 xg for 10 minutes (min) at 4 °C to separate the serum, which was then kept at −20 °C until analysis. Following euthanasia, kidney tissues were removed, immediately transferred into an Ribonucleic Acid (RNA) stabilization solution, and preserved at −80 °C (ILDAMLAB DF-360) for subsequent molecular procedures.

Ribonucleic Acid isolation and complementary Deoxyribonucleic Acid synthesis

Total Ribonucleic Acid was extracted from ~50 mg of kidney tissue using Trizol, followed by chloroform and isopropanol precipitation [13]. RNA quantity and purity were assessed by NanoDrop spectrophotometry (BioDrop, UK), and integrity was verified by 0.7 % agarose gel electrophoresis (FIG. 1). The synthesis of complementary Deoxyribonucleic Acid (DNA) was carried out employing the WizScript kit designed for reverse transcription (Wizbio, Korea).

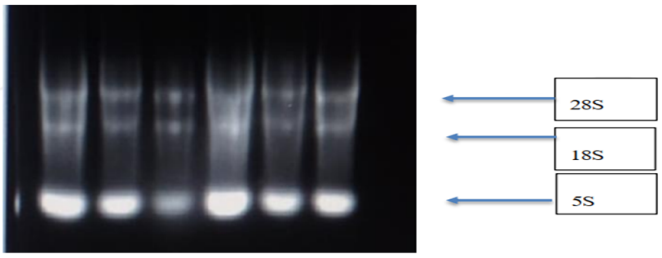

FIGURE 1. Ribonucleic acid integrity confirmation by agarose gel electrophoresis.

Quantitative Real-Time Polymerase Chain Reaction (Quantitative Reverse Transcription Polymerase Chain Reaction)

The transcriptional levels of the ER-related genes—including Xbp1, Perk, Ire1, Chop, Atf6, and Atf4—were quantified by Quantitative Reverse Transcription Polymerase Chain Reaction (qRT-PCR) (Qiagen, Rotor Gen, USA). Reactions were performed with SYBR Green–based master mix (ABT™ 2X PCR MasterMix, without dye, Türkiye) in combination with primers designed specifically for each target gene (TABLE I).

TABLE I
The base sequences of forward and reverse primers used in the Quantitative Reverse Transcription Polymerase Chain Reaction

Genes	L (5' to 3')	R (5' to 3')
Xbp1	rn-Xbp1-177bp-ID289754-F	CAGCAAGTGGTGGATTTGGA
	rn-Xbp1-177bp-ID289754-R	CCTTACTCCATTCCCCTTGGA
Chop	rn-Chop-103bp-ID29467-F	AACCTGAGGAGAGAGAAACCG
	rn-Chop-103bp-ID29467-R	TCATACCAGGCTTCCAGCTC
Perk	rn-Perk-162bp-ID29702-F	CTGAAGGACGAAAGCACAGAC
	rn-Perk-162bp-ID29702-R	ACAGGAAATGCCCACTGAGA
Ire1	rn-Ire1-265bp-ID498013-F	TGCGCAGGTGCAATGAC
	rn-Ire1-265bp-ID498013-R	GTAAAGGGAAGTTTCGTCAGGC
Atf6	rn-Atf6-217bp-ID304962-F	AGCCCCTCATTAACACGACA
	rn-Atf6-217bp-ID304962-R	TCACTCCCAGAATTCCTACTGATG
Atf4	rn-Atf4-135bp-ID79255-F	AGACACCGGCAAGGAGGAT
	rn-Atf4-135bp-ID79255-R	AACGTGGCCAAAAGCTCATC
Gapdh	rn-Gapdh-77bp-ID24383-F	AGTGCCAGCCTCGTCTCATA
	rn-Gapdh-77bp-ID24383-R	GGTAACCAGGCGTCCGATAC

The amplification reactions were prepared according to the manufacturer's recommendations (WizbioWizScript cDNA Synthesis Kit, Korea), but the components were assembled in a manner adapted for the experimental workflow. Each qPCR reaction had a final volume of 20 µL and consisted of the appropriate master mix, gene-specific primers, and the diluted cDNA template, with nuclease-free water added to achieve the designated reaction volume.

The thermal profile used for quantification followed a standard three-phase cycling strategy: an initial high-temperature step to activate the polymerase and denature the nucleic acids, a repeated sequence of brief denaturation and primer-dependent annealing/extension phases carried out for forty cycles, and finally a gradual temperature ramp for melt-curve inspection to ensure amplification specificity. Temperature settings for the annealing stage varied within a gene-dependent range of approximately 50–60 °C. Expression values were normalized against glyceraldehyde-3-phosphate dehydrogenase (GAPDH), which served as the internal reference transcript. Relative changes in mRNA abundance were computed using the comparative Ct framework originally proposed by Livak and Schmittgen [14].

Statistical analysis

Statistical evaluations were performed by summarizing the results as mean values accompanied by their standard errors (SE). Differences among the experimental groups were examined using a one-way analysis of variance, and when appropriate, Tukey's multiple comparison test was applied for post-hoc evaluation (SPSS software, version 22.0). A probability level below 0.05 was interpreted as evidence of a statistically meaningful difference.

RESULTS AND DISCCUSIONS

Blood glucose levels were significantly elevated in the IR group compared to the control ($P < 0.05$). Both quinoa-treated groups (IQ and QI) showed partial reductions, while the metformin-treated group (IM) exhibited values close to the control. The quinoa-only group (Q) maintained glucose levels comparable to controls.

The administration of DEX resulted in a significant increase in circulating insulin levels in all treated cohorts ($P < 0.05$). In rats, the combined administration of quinoa with DEX showed marginally reduced insulin levels compared with the IR group, while the metformin-treated group showed the lowest levels of insulin compared with all other DEX-treated cohorts ($P < 0.05$).

Expression analysis revealed marked upregulation (5,9 fold) of all ER stress-related genes in the IR group. Quinoa-treated groups showed significantly reduced expression levels ($P < 0.05$), closely aligning with those of the IM group. No significant gene expression changes were detected in the Q group relative to controls (TABLE II).

TABLE II
Relative expression levels of Endoplasmic Reticulum stress -related genes in rat kidney tissues (mean ± standard error)

	ER stress gene expression levels (mean ± standard error)					
	C	I	Q	IQ	QI	IM
Xbp1	1^{a}	$5,103 \pm 0,151^{c}$	$0,613 \pm 0,024^{a}$	$2,515 \pm 0,473^{b}$	$2,865 \pm 0,436^{b}$	$3,03 \pm 0,019^{b}$
Perk	1^{a}	$5,916 \pm 0,595^{d}$	$0,835 \pm 0,060^{b}$	$1,605 \pm 0,013^{c}$	$1,7 \pm 0,033^{c}$	$2,07 \pm 0,255^{c}$
Ire1	1^{a}	$4,47 \pm 0,471^{d}$	$1,2 \pm 0,175^{b}$	$1,49 \pm 0,168^{bc}$	$2,07 \pm 0,175^{c}$	$1,916 \pm 0,276^{bc}$
Chop	1^{a}	$4,12 \pm 0,456^{c}$	$1,34 \pm 0,130^{b}$	$1,79 \pm 0,060^{b}$	$1,945 \pm 0,217^{b}$	$1,516 \pm 0,078^{b}$
Atf6	1^{a}	$4,825 \pm 0,444^{d}$	$1,096 \pm 0,213^{b}$	$2,273 \pm 0,234^{c}$	$2,616 \pm 0,211^{c}$	$2,05 \pm 0,052^{c}$
Atf4	1^{a}	$4,236 \pm 0,909^{c}$	$1,286 \pm 0,236^{b}$	$1,983 \pm 0,095^{b}$	$2,37 \pm 0,143^{b}$	$2,405 \pm 0,064^{b}$

The distinction between the averages of the groups with varying letters in the same row is significant ($P < 0.05$). C: Control Group (Received standard chow and daily intraperitoneal (i.p.) injections of physiological saline for 13 d). I: Insulin Resistance Group (Fed standard chow for 13 d and received i.p. injections of dexamethasone 1 mg/kg/d), for the final 7 d to induce insulin resistance. Q: Quinoa Group (Fed a quinoa-supplemented diet for 6 d, followed by standard chow and saline injections for the subsequent 7 d). IQ: IR + Quinoa Group (Insulin resistance was induced with DEX (1 mg/kg/d, i.p.) for 7 d, followed by a 6-d treatment period with the quinoa-supplemented diet). QI: Quinoa + IR Group (Fed the quinoa-supplemented diet for 6 d (prophylactic treatment), followed by 7d of DEX injections). IM: IR + Metformin Group (Insulin resistance was induced with DEX (1 mg/kg/d, i.p.) for 7 d, followed by a 6-d treatment period with metformin (40 mg/kg/d, oral gavage) while being fed standard chow).

The highest HOMA-IR index was observed in the IR group ($P< 0.05$). Although this index declined in the IQ, QI, and IM groups, it remained higher than control values in the quinoa-treated animals ($P < 0.05$). The quinoa-only group did not differ significantly from the controls in terms of insulin sensitivity (TABLE III, and FIGS. 2 and 3).

TABLE III
Blood glucose, insulin, and Model Assessment of Insulin Resistance levels in experimental groups (mean ± standard error)

	C	I	Q	IQ	QI	IM
Glucose (mg/dl)	122,17 ± 5,77a	259,64 ± 37,59b	124,29 ± 2,14a	193,9 ± 34,88ab	202,04 ± 28,29ab	121,37 ± 42,27a
Insulin (pg/ml)	9,53 ± 0,29a	11,02 ± 1,57ab	10,74 ± 0,94ab	11,41 ± 1,07b	11,61 ± 1,56b	10,80 ± 0,66ab
HOMA-IR	2,88 ± 0,13a	7,11 ± 1,12b	3,29 ± 0,12a	6,33 ± 1,04b	6,57 ± 1,25b	3,26 ± 0,82a

Different letters within a row indicate statistically meaningful differences between the group means ($P < 0.05$). C: Control Group (Received standard chow and daily intraperitoneal (i.p.) injections of physiological saline for 13 d). I: Insulin Resistance Group (Fed standard chow for 13 d and received i.p. injections of dexamethasone 1 mg/kg/d), for the final 7 d to induce insulin resistance. Q: Quinoa Group (Fed a quinoa-supplemented diet for 6 d, followed by standard chow and saline injections for the subsequent 7 d). IQ: IR + Quinoa Group (Insulin resistance was induced with DEX (1 mg/kg/d, i.p.) for 7 d, followed by a 6-d treatment period with the quinoa-supplemented diet). QI: Quinoa + IR Group (Fed the quinoa-supplemented diet for 6 d (prophylactic treatment), followed by 7d of DEX injections). IM: IR + Metformin Group (Insulin resistance was induced with DEX (1 mg/kg/d, i.p.) for 7 d, followed by a 6-d treatment period with metformin (40 mg/kg/d, oral gavage) while being fed standard chow).

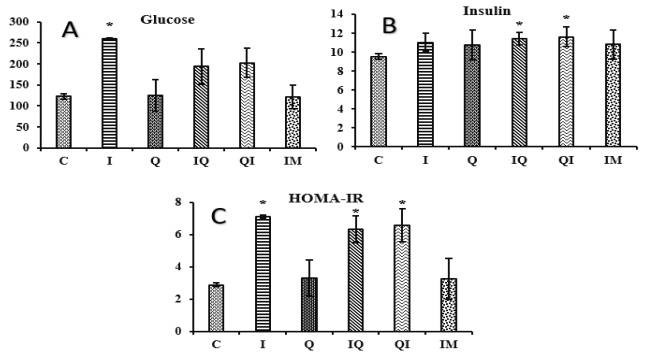

FIGURE 2. Biochemical results of the groups. C: Control Group (Received standard chow and daily intraperitoneal (i.p.) injections of physiological saline for 13 d). I: Insulin Resistance Group (Fed standard chow for 13 d and received i.p. injections of dexamethasone 1 mg/kg/d), for the final 7 d to induce insulin resistance. Q: Quinoa Group (Fed a quinoa-supplemented diet for 6 d, followed by standard chow and saline injections for the subsequent 7 d). IQ: IR + Quinoa Group (Insulin resistance was induced with DEX (1 mg/kg/d, i.p.) for 7 d, followed by a 6-d treatment period with the quinoa-supplemented diet). QI: Quinoa + IR Group (Fed the quinoa-supplemented diet for 6 d (prophylactic treatment), followed by 7d of DEX injections). IM: IR + Metformin Group (Insulin resistance was induced with DEX (1 mg/kg/d, i.p.) for 7 d, followed by a 6-d treatment period with metformin (40 mg/kg/d, oral gavage) while being fed standard chow)

The present study investigated the protective effects of quinoa supplementation on renal ER stress in a DEX-induced IR rat model. These findings demonstrate that quinoa significantly ameliorates both the systemic metabolic dysfunction and the molecular markers of ER stress in the kidney, suggesting its potential as a supportive dietary component in IR-associated nephropathy.

Studies conducted on rats fed diets containing quinoa prepared in various forms with a high content of added simple carbohydrates found that the glycemic index, blood sugar levels, lipid levels, accumulation of epididymal fat tissue, and total food intake were all reduced [15]. In patients at risk of diabetes, studies have shown that processed quinoa can reduce HbA1c and body mass index levels, keep fasting plasma glucose levels steady, and make you feel fuller for longer [16]. The results observed in this study agree with previous studies demonstrating that DEX causes the development of IR in the rat, based upon elevated levels of fasting glucose, insulin, and HOMA-IR values in the IR group (TABLE III). Subsequently, the elevated value of HOMA-IR of 4.5 ± 0.2 in the IR group was indicative of a state of severe metabolic distubance when compared with the HOMA-IR of the control group (1.0 ± 0.1).

According to the this research, supplementation with quinoa effectively lessens the amount of DEX-induced kidney ER stress. In this study, it was shown that there is a statistically significant inverse correlation between levels of HOMA-IR after treatment with quinoa compared to treatment with DEX (decreased HOMA-IR) and decreased gene expression of ER stress.

Quinoa has the potential to affect cellular stress via direct modulation of gene expression, particularly through Xbp1, Perk and Chop regulation. The findings also affirm findings on previous evidence that quinoa can improve metabolic parameters and reduce inflammation [17 , 18 , 19]. Additionally, DEX, as a strong glucocorticoid hormone, is known to influence ER stress signaling pathways [5]. Through DEX, misfolded proteins accumulate and calcium homeostasis is disrupted, directly activating each of the main UPR sensors (PERK, IRE1, and ATF6) [20].

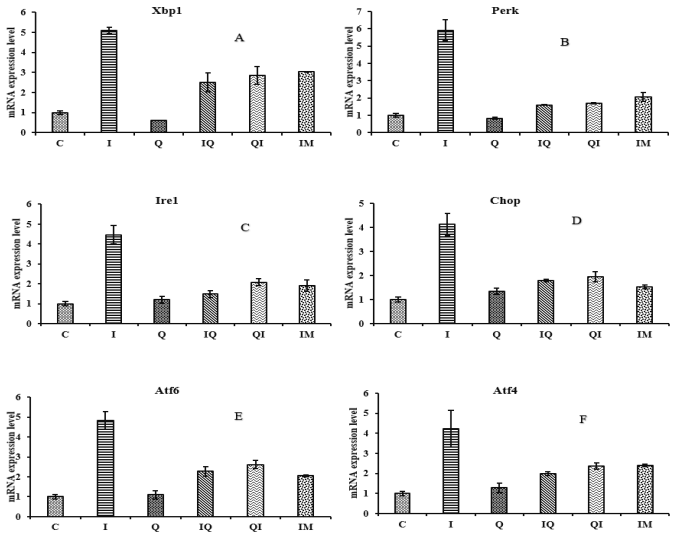

FIGURE 3. Gene expression results of the groups. C: Control Group (Received standard chow and daily intraperitoneal (i.p.) injections of physiological saline for 13 d). I: Insulin Resistance Group (Fed standard chow for 13 d and received i.p. injections of dexamethasone 1 mg/kg/d), for the final 7 d to induce insulin resistance. Q: Quinoa Group (Fed a quinoa-supplemented diet for 6 d, followed by standard chow and saline injections for the subsequent 7 d). IQ: IR + Quinoa Group (Insulin resistance was induced with DEX (1 mg/kg/d, i.p.) for 7 d, followed by a 6-d treatment period with the quinoa-supplemented diet). QI: Quinoa + IR Group (Fed the quinoa-supplemented diet for 6 d (prophylactic treatment), followed by 7d of DEX injections). IM: IR + Metformin Group (Insulin resistance was induced with DEX (1 mg/kg/d, i.p.) for 7 d, followed by a 6-d treatment period with metformin (40 mg/kg/d, oral gavage) while being fed standard chow)

The development of systemic IR and subsequent metabolic overload are conducive to establishing a state glucotoxicity/lipotoxicity within the kidneys. This glucotoxicity/lipotoxicity surpasses the ER folding capacity, resulting in an increase in the activation of the UPR which leads to an increase in the expression of the pro-apoptotic transcription factor CHOP [20]. The fourfold increase in the levels of Chop expression in the IR group is a key marker of unresolved ER stress suggesting that renal cells are likely undergoing apoptosis [21]. The upregulation of these genes is closely associated with diabetic nephropathy and renal fibrosis, thereby supporting the relevance of this model to renal pathology in humans [22].

The metabolic condition associated with HOMA-IR has dramatically decreased to a mean value of 2.1 ± 0.1 for the IQ group (TABLE III). In conjunction with this change in metabolic condition, there has been a fourfold upregulation of the CHOP gene expression in relation to the IR condition; however, there is a 60 % attenuation of the fourfold upregulation of CHOP gene expression in the quinoa-treated groups (FIG. 3). Thus, the improvement of the metabolic condition validates that quinoa ameliorates the underlying stress mechanism from the UPR. One possible explanation for quinoa's ability to ameliorate the underlying stress mechanism is due to the rich bioactive content present in Chenopodium quinoa [23 , 24].

The decrease in ER stress could be due, in part, to the antioxidant effects of quinoa: its glycemic index is low, which leads to less severe oxidative stress and inflammation associated with ER stress [7 , 9 , 25]. Previous research has shown that quinoa has a role in modifying many signaling pathways related to ER stress, thus supporting the findings of this study [26]. The Perk-Atf4-Chop pathway is an important part of the ER stress response and has been shown to be involved in apoptosis, particularly in many different types of kidney disease. Since the ER stress response may provide some level of protection from certain types of kidney disease, the autophagic process through which misfolded proteins are degraded has also been identified as helpful for certain types of nephron damage associated with ER stress [18 , 27 , 28 , 29 , 30]. Quinoa may offer some of the same protective benefits to the (IQ and QI) groups as does the IM group, in a way to reduce insulin resistance and gene expression of ER stress markers.

The three primary mediators involved in transducing the signal from ER stress to the appropriate adaptive responses (Atf6, Perk, and Ire1) require activation via the ER stress response pathway, and, as a result, are implicated in supporting the process of cellular survival following ER stress. Conversely, if cells are unable to resolve their ER stress they may go through cellular dysregulation and apoptosis [31 , 32].

Quinoa polyphenols and saponins can directly modulate the UPR by enhancing protein folding capacity and increasing cellular antioxidant capacity through alleviation of ER stress. The alleviation of ER stress is reflected by a reduction in expression of all six ER stress gene markers, as seen in the quinoa-treated groups.

Although the current study provides robust evidence of the presence of these adaptive responses in mRNA, it does not validate the mRNA-regulated protein markers of the adaptive responses (e.g., by Western Blotting) and therefore does not conclude that the observed change in the mRNA will also manifest as a change in the protein measures (e.g., CHOP, p-PERK, GRP78). Further, the reduction of apoptosis and fibrosis (i.e., the identification and confirmatory analysis) should be confirmed via histopathological examination.

CONCLUSION

This study demonstrates that quinoa supplementation effectively mitigates DEX-induced systemic insulin resistance and the resulting renal ER stress, evidenced by the significant downregulation of the pro-apoptotic Chop gene. Quinoa's protective mechanism, likely through its bioactive compounds, offers a promising dietary strategy for managing IR-associated renal complications.

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Conflict of interest

The authors declare no conflict of interest.

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