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Protective Role of Quercetin Against Acrylamide-Induced Toxicity in Male Rats

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A B S T R A C T

This study aims to evaluate the protective role of quercetin (QE) against acrylamide-induced toxicity on male rats. QE plays important roles in human health by virtue of its antioxidant activity. The possible ameliorative effect of QE on serum levels of fasting blood sugar (FBS), glycosylated hemoglobin (HbA1c), lipids profile, and thyroid gland and pituitary hormones in male rats was investigated. Fifty adult male albino rats were divided into five groups. The first group served as normal control, the second group received 20 mg/kg acrylamide (ACR), the third group received 20 mg/kg ACR plus 100 mg/kg QE, the fourth group received 20 mg/kg ACR plus 50 mg/kg QE and the fifth groups received 100 mg/kg QE alone. ACR and QE were given by oral administrations for 30 days. Our results indicated that ACR administration induced significant elevation in serum level of FBS, glycosylated hemoglobin (HbA1c), total cholesterol (TC), triglycerides (TG) and HDL-C, whereas, LDL-C levels was reduced. Also, ACR-intoxication significantly reduced serum levels of free and total T3 as well as free and total T4, while significantly elevated serum level of follicle stimulating hormone (FSH), luteinizing hormone (LH) and thyroid stimulating hormone (TSH). QE significantly normalized the previous parameters. Thus, the study showed that QE exerts a protective effect against ACR toxicity on male rats. Based on its beneficial effect on health, a daily consumption of food containing QE is recommended.

Introduction

Quercetin is one of several naturally-occurring dietary flavone compounds belonging to a broad group of polyphenolic flavonoid substances. In plants, the flavonolaglycone is most commonly present conjugated at the 3- position of the unsaturated ring with a sugar moiety, forming O-b-glycosides such as quercetin [1]. Flavones exhibit numerous biological and pharmacological effects, including anti-oxidant, chelation, anti-carcinogenic, cardioprotective, and bacteriostatic properties [2,3]. In plants, these compounds exhibit strong anti-oxidant properties, possibly protecting plants against harmful ultraviolet rays [4].
Quercetin possesses various biological functions including, anti-inflammatory, anti-coagulation, oxygen radical-scavenging activities [5]. QE effectively suppressed inflammation and oxidative stress induced by lipopolysaccharides [6]. Middleton *et al.* [2] and Erlund [7] showed that QE has anti-oxidant, anti-carcinogenic, anti-inflammatory and cardio-protective properties. Several authors have related the anti-carcinogenic and anti-inflammatory effects to the anti-oxidant and free radical scavenging properties of QE [8,9]. Middleton *et al.* [2] also stressed the anti-carcinogenic properties of QE and other flavonoids. Galati and O'Brien [10] also showed the ability of certain flavonoids to prevent tumor development and also raised the possibility of flavonoid-drug interactions. It remains to be determined whether these properties of QE are affected independently or share a common mechanism of action. The anti-oxidant properties are largely a function of the chemical structure of QE, particularly the presence and location of the hydroxyl (-OH) substitutions [9].
Acrylamide is a dietary contaminant and environmental toxicant. Assessment of the presence of acrylamide is a great concern in many countries. According to the results obtained so far, potato products account for around 50% and baking products and bread for around 20% of human [11]. Several observations have led to the hypothesis that heating of food could be an important

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source of human exposure to acrylamide. It is formed when heating/frying is done in an oven, on a frying pan or by microwave heating, whilst no acrylamide has detected in boiled food products [12]. Therefore, detection of acrylamide in food has become a very important issue in food safety. The average daily intake of ACR in western countries was estimated to be in the range of 3.4 mg/kg BW among younger age groups. Children eat more acrylamide than adults probably because of their higher caloric intake relative to body weight as well as their higher consumption of certain acrylamide-rich foods, such as French fries and potato crisps [13].

Acrylamide is rapidly absorbed from the gastrointestinal tract following oral administration and it is rapidly absorbed into the circulation and thereafter distributed to various organs, reacts with cellular DNA, hemoglobin, nerve cells and enzymes [14]. The toxicity of acrylamide involves the enhancement of cellular oxidative stress by depleting glutathione which is the major cellular antioxidant, generation of reactive oxygen species and DNA damage [15].

The acrylamide toxicity is considered to be hepatotoxic and causes lipid peroxidation [16]. Acrylamide have significant binding capacity to brain [17]. Neurotoxicity of acrylamide is well established in humans and experimental models. It is known to affect both central and peripheral nervous system, hampering various sensory and motor functions [18]. Acrylamide neurotoxicity in both laboratory animals and humans is characterized by ataxia and distal skeletal muscle weakness [19]. However, ACR intoxication in rodent models is associated with selective nerve terminal damage in both central and peripheral nervous systems. A growing body of evidence indicates that the nerve terminal is a primary site of ACR action and that inhibition of corresponding membrane fusion processes impairs neurotransmitter release and promotes eventual degeneration [18].

ACR-induced oxidative stress in nervous system (brain, spinal cord and sciatic nerve) and sensory and motor dysfunction in rats [20]. ACR significantly reduced the proliferation of mouse neuronal progenitor cells and induced apoptotic cell death via elevation in the reactive oxygen species [21]. However, ferulic acid ameliorated the toxic effect of acrylamide-induced inflammation and oxidative stress in brain and testes [22, 23]. The current study was designed to investigate the protective role of quercetin on the toxicity of acrylamide-induced blood sugar, glycosylated hemoglobin, lipids profile, thyroid gland and six hormones in rats.

Materials and Methods

Chemicals: Acrylamide was purchased from Merk-Schuchardt Chemical Company (Hohenbrunn, Germany), with purity of 99%. Quercetin was obtained from Sigma Chemical Company. All other chemicals were of analytical grade.

Experimental animals: Fifty male albino rats weighing between 180 -190 g were used for the present study. The rats were obtained from the animal house of the National Organization for Drug Control and Research, Egypt. The animals were kept under standard laboratory conditions of light/dark cycle (12h/12 h) and temperature (20-25◦C) for one week. They were provided with a nutritionally adequate basal laboratory diet. The basal diet consists of casein (10%), cotton seed oil (4%), salt mixture (4%), vitamin mixture (1%), carbohydrates (sucrose and starch 1:1, 80.8%) and choline Chloride (0.2%) [24].

Grouping of animals: Rats were divided into 5 groups of 10 rats each as follows; Group 1: Normal control (NC): rats were feeding basal diet. Group 2: rats were received 20mg/kg oral ACR alone. Group3: rats were received 20mg/kg ACR with 100 mg/kg QE. Group 4: rats were received 20mg/kg ACR with 50 mg/kg QE. Group 5: rats were received 100 mg/kg QE alone. ACR and QE were given daily by oral gavage administration for 30 days. Dose of acrylamide was according to Abdel-Daim et al. [24], whereas doses of quercetin were according to Dwivedi and Flora [25] with modification. Blood samples were collected after 30 days at the end of the experiment. Animal experiments were conducted according to the guidelines of institutional animal care and use ethical committee.

Handling of Blood Samples: At the end of each experimental period, all rats were fasted for 12 hours and then anesthetized with diethyl ether and abdominally dissected. Blood samples were collected from venous sinus in centrifuge tubes to separate serum by centrifugation at 3000 rpm for 15 minutes. Sera were kept at -20°C pending assays.

Serum glucose concentration was determined using Sentinel kits based. Glycosylated hemoglobin (HbA1c) was determined by the colorimetric method according to Sudhakar and Pattabiraman [26]. Serum cholesterol, Triglycerides and HDL-cholesterol levels were determined using kits developed by Diamond Diagnostics, Egypt. Serum LDL-cholesterol concentration was calculated according to Friedewald *et al.* [27]. Serum levels of Tri-iodothyronine (T3), thyroxine/ Tetraiodothyronine (T4) and thyroid stimulating Hormone (TSH) were determined using commercially available radioimmunoassay kits (Cat. Nos. ABIN4888531, ABIN4888533 and ABIN5618313, respectively, Monobind, Inc, CA, USA). Serum levels of FT3 and FT4 were determined using commercially available enzyme-linked immunosorbent assay kits (Cat. Nos. ABIN5671039 and ABIN2533587 respectively, Monobind, Inc, CA, USA). Serum levels of FSH and LH were determined by enzyme-linked immunosorbent assay kits (Cat. Nos. ABIN365553 and ABIN365711, Monobind, Inc, CA, USA).

Statistical analysis: The data were expressed as mean ± SE. Differences between groups were assessed by one-way analysis of variance (ANOVA) using the statistical package for social sciences software package (SPSS) for Windows (version 13.0).

Results

The results of the statistical analysis indicated a significant increase ($p < 0.05$) in serum levels of FBG and glycosylated hemoglobin (HbA1c) in group intoxicated with ACR compared to control group. Meanwhile, QE treated rats in group 3 and group 4 exhibited significant reductions in FBG and HbA1c levels compared to the group of rats receiving ACR alone (**Fig. 1**).

Administration of 20 mg acrylamide/Kg significantly elevated serum levels of total cholesterol, triglyceride and LDL-C in male albino rats when compared to control group (**Figs. 2 and 3**). On the other hand, ACR administration caused a significant decrease in HDL-C ($p < 0.05$) level compared to control group (**Fig. 3**). Meanwhile, the administration of QE plus ACR in groups 3 and 4 showed significant lowering effects on serum levels of total cholesterol, triglycerides and LDL-C and elevating effect on serum HDL-C level when compared to the group 2 of rat receiving ACR alone (**Figs. 2 and 3**).

There were significant decreases in T3 and T4 levels in group intoxicated with 20 mg/kg acrylamide alone compared to control group as well as significant increase in TSH level. QE treatment in groups 3 and 4 caused significant elevation in T3, T4 levels up to the normal, and lowered the elevated level of TSH compared to group 2; also, groups treated with QE showed non-significant difference from control group. There were also significant decreases in FT3 and FT4 levels in group 2 compared to control group. On the other hand, QE given to group 3 and 4 showed normalization effect on FT3 and FT4 levels compared to untreated group, and they also showed non-significant difference with control group (**Table 1**).

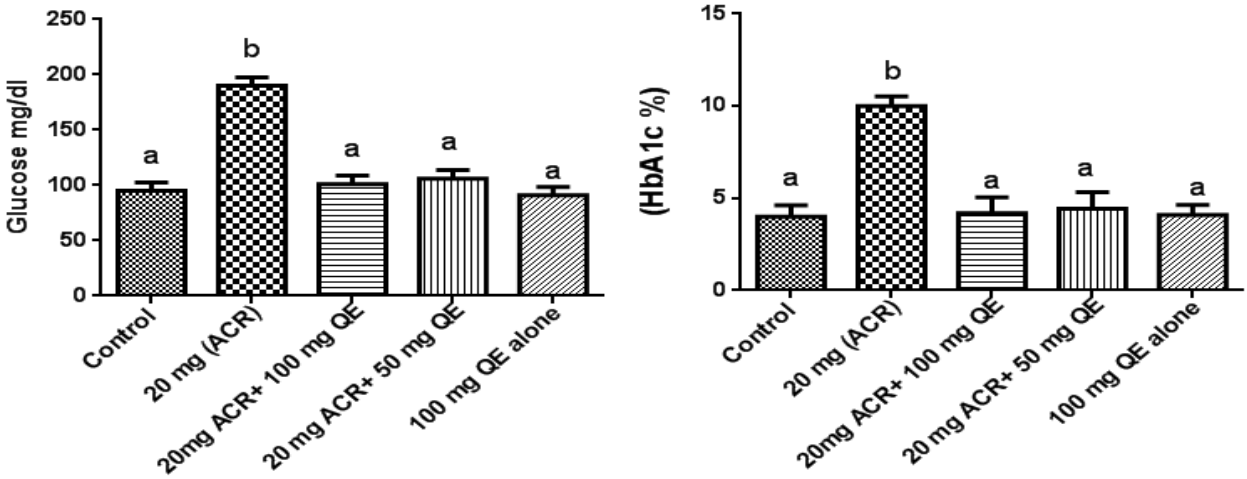

Fig 1: Effect of quercetin on glucose and Glycosylated hemoglobin in rats intoxicated with acrylamide for 30 days. Each value represents the mean ± S.E (standard error) and the mean of fifth replicates to each sample. Values in the same column with the same letter are not significant at $p \leq 0.05$.

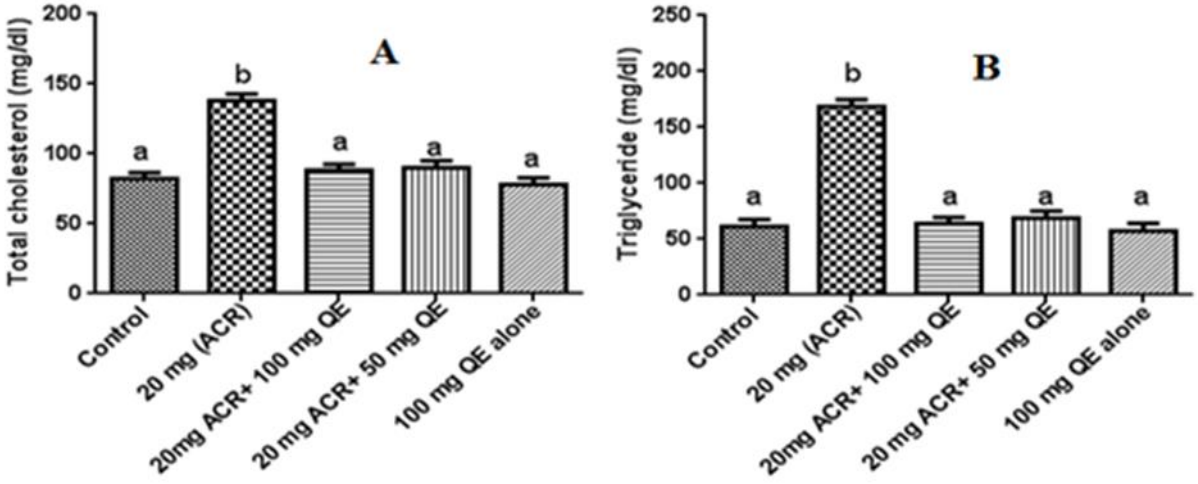

Fig 2: Effect of quercetin on lipid profile in rats intoxicated with acrylamide for 30 days. Each value represents the mean ± S.E and the mean of fifth replicates to each sample. Values in the same column with the same letter are not significant at $p \leq 0.05$.

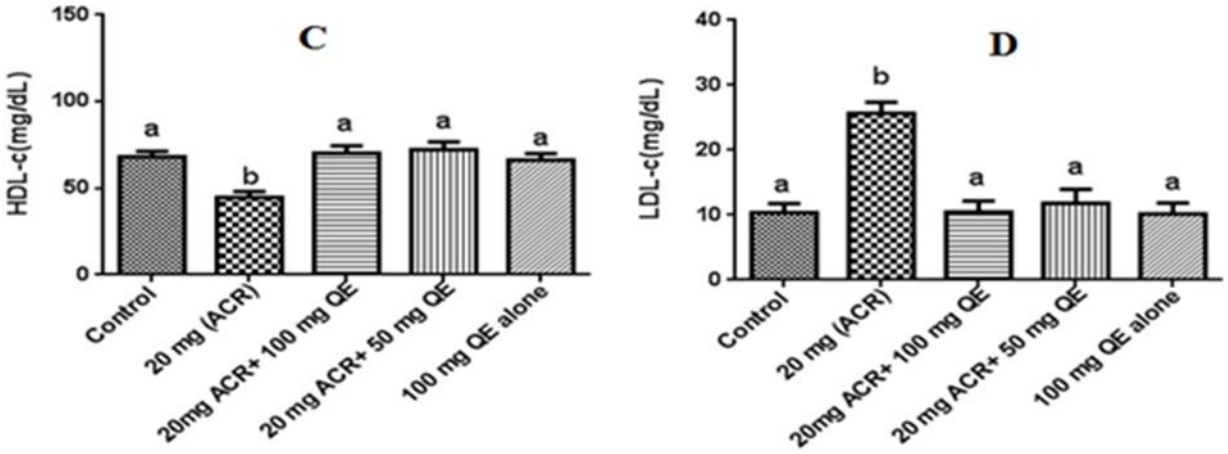

Fig 3: Effect of quercetin on lipid profile in rats intoxicated with acrylamide for 30 days. Each value represents the mean ± S.E and the mean of fifth replicates to each sample. Values in the same column with the same letter are not significant at $p \leq 0.05$.

Table 1. Effects of quercetin on thyroid hormones levels in male albino rats (Mean ± SE)

	Thyroid gland hormones				
Groups	**T3 (ng/dl)**	**Free T3 (pg/ml)**	**T4 (µg/dl)**	**Free T4 (ng/dl)**	**TSH (µIU/ml)**
Control	181.60 ± 1.73[a]	3.8 ± 1.23 [a]	10.45 ± 0.20 [a]	1.32 ±0.85 [a]	0.12 ± 0.08 [a]
20 mg (ACR)	131.51 ± 2.09[b]	1.16 ± 0.96 [b]	6.45 ± 0.19 [b]	0.91 ±0.43 [b]	0.26 ± 0.03 [b]
20mg ACR+ 100 mg QE	184.38 ± 1.43 [a]	3.69 ± 0.46 [a]	10.53 ± 0.09 [a]	1.28± 0.62 [a]	0.14 ± 0.06 [a]
20 mg ACR+ 50 mg QE	190.41 ± 1.73 [a]	3.41± 0.1.17 [a]	10.61 ± 0.15 [a]	1.17 ± 0.21 [a]	0.18 ± 0.08 [a]
100 mg QE alone	178.60 ± 2.41 [a]	3.88 ± 0.29 [a]	10.41 ± 0.18 [a]	1.33 ± 0.31 [a]	0.10 ± 0.08 [a]

Values are mean± SE of 6 rats. Values with the same letters are not significant at (P≤0.05). ACR = acrylamide, QE = Quercetin. Values on the same column not sharing the same superscript letters were significantly different ($p < 0.05$).

Regarding FSH and LH, there were significant increases in ACR intoxicated group compared to control group. The data in **Fig. 4** revealed that serum levels of follicle stimulating hormone (FSH) and luteinizing hormone (LH) decreased significantly in rats treated with QE plus ACR when compared to ACR intoxicated group.

Regarding all parameters, there were no significant differences between the two groups of rats treated with different doses of QE. Also, rats treated with QE alone showed normal levels regarding all parameters.

Discussion

The present study showed elevation in blood glucose and glycosylated hemoglobin levels in group intoxicated with acrylamide. These results agree with Totani *et al.* [28] who reported low serum insulin levels in rats which received ACR, which could be the reason for the high blood sugar levels in the ACR groups of the current study. On the other hand, group receiving 20 mg/kg acrylamide plus50 and 100 mg /kg QE showed ameliorative effect in serum glucose level compared to group receiving 20 mg /kg acrylamide alone. Quercetin protects organisms against several types of diseases [29] and elicits beneficial effects on glucose and lipid metabolism [30]. Euonymus Alatus as a folk medicine in China has been clinically used to treat type 2 diabetes, and to alleviate hyperglycemia in animals with diabetes. Flavonoid can effectively attenuate hyperglycemia in alloxan-induced diabetic mice [31]; however, its concrete mechanisms remain unclear.

Lipids have structural and functional important roles in different body organs and cells. The lipid is an important part of healthy body because it is used to form cell membranes, several hormones and is necessary for other cellular function.

In the current study, ACR causes significant increases in the levels of total cholesterol, triglyceride and LDL-C in ACR group, and significant decreases in the level HDL-C compared to the control group. Since lipid metabolism, such as production of triglyceride and cholesterol synthesis, takes place partially in the liver and it has been

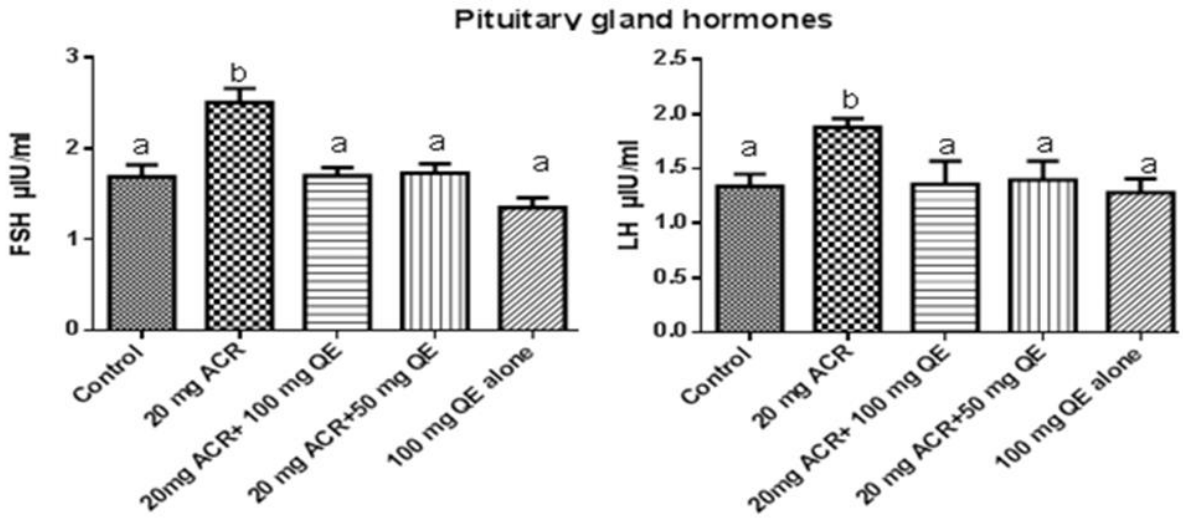

Fig 4: Effect of quercetin on pituitary gland hormones levels in rats intoxicated with acrylamide for 30 days. Each value represents the mean ± S.E and the mean of fifth replicates to each sample. Values in the same column with the same letter are not significant at $p \leq 0.05$.

documented that ACR causes liver damage [32]; this leads to an increase in the synthesis of plasma lipoproteins and high mobilization of lipids from the liver. Consequently, the results can be explained by the ACR involvement in lipid peroxidation [33]**.** Allam *et al*. [34] and Rawi*et al.* [35] who indicated that the strong reducing effects of acrylamide on serum total cholesterol, triglycerides, and LDL-C levels may be due to the high levels of trans-fat in most fried food and many common bakeries like bread. Tran's fats clearly raise the LDL-C.

On the other hand, quercetin treated groups showed a lipid lowering effects. Other studies have reported that QE-rich supplementation reduces serum concentrations of total cholesterol but increases serum concentrations of HDL-cholesterol [36-38] which is in agreement with the results of the present study. Several explanations were suggested of how quercetin is able to influence serum lipid profile. Igarashi and Ohmuma [39] stated that quercetin decreases serum total cholesterol level in rats through increasing its fecal excretion. It was also reported that quercetin reduces de novo synthesis of fatty acids and consequently cholesterol biosynthesis and lipoproteins formation [37].

Our results indicated that, there were significant decreases in T3, FT3, T4 and FT4 serum levels in group receiving acrylamide alone compared to respective control group. Our result also revealed significant increase in TSH serum level in this group compared to control group. The present study exhibited changes in the levels of the thyroid hormones and this result is consistent with Sharma and Jain [40] who reported that decrease in T3 and T4 levels and a consequent increase in TSH were observed**.** The thyroid hormones control the skeletal and mental growth along with cell respiration, thus the above morphological toxic effects of ACR are congruent with the above results of T3, T4 and TSH.

Thyroid hormones are recognized as catabolic hormones and they regulate various processes of metabolism [41]**.** The relationship between thyroid hormones and lipid metabolism is clearly displayed in patients suffering from thyroid dysfunctions. Overt hypothyroid patients show elevated cholesterol and triglycerides levels while overt hyperthyroid patients show reduced lipid levels**.** These observations have been shown to extend into the subclinical hypo/hyperthyroid range [42], suggesting that apart from thyroid hormones, TSH exerts independent effects on lipid metabolism.

On the other hand, the group which received 20 mg/kg acrylamide plus100 and 50 mg /kg quercetin showed ameliorative effect on T3, T4 and TSH levels compared to group treated 20 mg /kg acrylamide alone. The ameliorative effect of quercetin on acrylamid-induced alteration might be due to its antioxidant activity. Quercetin is one of the most frequently studied bio-flavonoids in its class of flavonols. Quercetin is present in high concentrations in fruits and vegetables such as tea, apples, mulberries, onions, potatoes, and broccoli. It has been shown to have high potent antioxidant and cytoprotective effects in preventing endothelial apoptosis caused by oxidants [43]**.** Quercetin is a more potent antioxidant than other antioxidant nutrients, such as vitamin C, vitamin E, and β-carotene, and it can chelate transition metal ions, including iron, thus preventing the iron-catalyzed Fenton reaction [44].

In Our study, FSH and LH serum levels were significantly increased in group treated 20 mg/kg acrylamide alone compared to control group non-treated. These results are similar to Abd El-Mottaleb *et al*. [45] who indicated that serum FSH and LH levels significantly increased in acrylamide group may be due to insufficient level of testosterone which initiates a negative feedback mechanism**.** Free and total testosterone have been assessed in previous study of one of the coauthors and showed a decline in serum under the same experimental conditions [46]. Collodel *et al.* [47] reported that increase in

stress hormones, such as cortisol, leading to a subsequent decrease in another hormone called gonadotropin releasing hormone (GnRH). GnRH is made in the hypothalamus and it plays a role in the production of key hormones namely LH and FSH that can affect the quality and quantity of sperm. This stress/fertility link has been fairly well established in past years.

On the other hand, the groups which received 20 mg/kg acrylamide plus100 and 50 mg /kg quercetin showed ameliorative effect on hormones levels of LH and FSH compared to group receiving 20 mg /kg acrylamide alone. This finding is in agreement with Khaki *et al. [*[48]] who found that quercetin increased serum testosterone levels and had beneficial effects on sperm parameters in streptozotocin-induced diabetic male rats**.** Also, Ma *et al.* [49] reported that quercetin can increase serum testosterone levels in male rats**.** One of co-authors showed that quercetin provides protection against oxidative stress and damage caused by acrylamide at the tissue level and various body organs including the male reproductive system [46]**.** The results of some studies demonstrated the importance and efficacy of flavonoids in reducing the toxicity of anticancer drugs and fertility parameters [49, 50]**.** Quercetin also works to inhibit the enzyme xanthine oxidase, which is the main enzyme in the process of lipid peroxidation and thus prevents this process and protects the cell membrane and mitochondria. This enzyme is one of the enzymes that mediate the process of generating free radicals [47]**.** Recently, Nna et al**.** [51] found that all three models of quercetin treatment (pre-treatment, post-treatment and simultaneous treatment) against cadmium chloride-induced oxidative stress, decreased MDA, H_2O_2, and increased SOD, CAT and GPx activities in the uterus and ovaries, decreased apoptosis of follicular cells, and increased serum reproductive hormones. However, the quercetin pre-treated model offered better protection against $CdCl_2$ relative to the other two models**.** These results suggest an antioxidant and anti-apoptotic actions of quercetin as well as an ameliorative effect on ovaries exposed to oxidative stress.

Conclusion

In this study, we evaluated the protective effects of quercetin, an antioxidant agent, against acrylamide-induced toxicity in male rats. We found that this antioxidant modulated the following altered serum biochemical parameters: glucose, glycosylated hemoglobin, lipids profile, thyroid gland and pituitary hormones in intoxicated rats. So, based on its beneficial effects on human health, we recommend daily consumption of foods containing QE.

References

1) **Merck (2001).** Quercetin. The Merck Index: An Encyclopedia of Chemicals, Drugs, and Biologicals, 13th ed. Merck and Co., Inc., Whitehouse Station, New Jersey, p. 1438 (Abstract no. 8122).
2) **Middleton, Jr. E., Kandaswami C. and Theoharides, T. C. (2000).** The effects of plant flavonoids on mammalian cells: implications for inflammation, heart disease and cancer. Pharmacol. Rev. **42**(4):673-751.
3) **PDRNS (2001).** Quercetin. In: Physicians' Desk Reference for Nutritional Supplements, 1st Ed. Physicians' Desk Reference (PDR), Demoines, Iowa/Medical Economics Data Production Company, Montvale, New Jersey, p. 390-392.
4) **Wiczkowski, W., Nemeth, K., Bucinski, A. and Piskula, M. K. (2003).** Bioavailability of quercetin from flesh scales and dry skin of onion in rats. Pol. J. Food Nutr. Sci. **12**:95-99.
5) **Yu, P. X., Zhou, Q. J, Zhu, W. W., WU, Y. H., WU, L. C., Lin, X., Chen, M. H. and QIU, B. T. (2013).** Effects of quercetin on LPS-induced disseminated intravascular coagulation (DIC) in rabbits. Thromb. Res. 131:270-273.
6) **Huang, R., Zhong, T. and WU, H. (2015).** Quercetin protects against lipopolysaccharide-induced acute lung injury in rats through suppression of inflammation and oxidative stress. Arch. Med. Sci. **11**(2):427-432.
7) **Erlund, I. (2004).** Review of the flavonoid's quercetin, hesperetin and naringenin. Dietary sources, bioactivities, and epidemiology. Nutr. Res. **24**:851–874.
8) **Stavric, B. (1994).** Quercetin in our diet: From potent mutagen to probable anticarcinogen. Clin Biochem. **27**:245-248.
9) **Formica, J. V. and Regelson, W. (1995).** Review of the biology of quercetin and related bioflavonoids. Food Chem. Toxicol. **33**:1061-1080.
10) **Galati, G.and O'Brien, P.J. (2004).** Potential Toxicity of flavonoids and other dietary phenolics: significance for chemopreventive and anticancer properties. Free Radic. Biol. Med. **37**(3):287–303.
11) **Keramat, J., LeBail, A., Prost, C. and Jafari, M. (2011).** Acrylamide in Baking Products. Food Bioproc Tech., **4**:530–543.
12) **Torqvist, M. (2005).** Acrylamide in food, The discovery and its Implications, Chemistry and safety of acrylamide in food, Springer Science and Business Media Inc., p.1–19.
13) **Dybing, E., Farmer, P., Andersen, M. and Fennell, T. (2005).** Human exposure and internal dose assessments of acrylamide. Food Chem Toxicol., **43**:365-410.
14) **Rayburn, J. and Friedman, M. (2010).** l-cysteine, n-acetyl-l-cysteine and glutathione protect Xenopus laevis embryos against acrylamide-induced malformations and mortality in the frog embryo teratogenesis assay, J. Agric. Food Chem., **58**(20): 11172-11178.
15) **Mei, N., Hu, J., Churchwell, M., Guo, L., Moore, M., Doerge, D. and Chen, T. (2008).** Genotoxic effects of acrylamide and glycidamide in mouse lymphoma cells. Food Chem Toxicol., **46**:628-636.
16) **Abou-Donia, M., Ibrahim, J., Corcoran, L., Lack, A., Friedman, M. and Lapadula, M. (1993).**

Neurotoxicity of glycidamide and acrylamide metabolite following intraperitoneal injection in rats. Toxicol and Environ. Health, **39**: 447-464.

17) **Sumner, S., Selvaraj, L., Nauhaus, S. and Fennell, T. (1997).** Urinary metabolites from F344 rats and B6c3F1 mice coadministered acrylamide and acrylonitrile for 1 or 5 days. Chem Res Toxicol., **10**:1152-1160.
18) **LoPachin, R.and Gavin, T. (2008).** Acrylamide-induced nerve terminal damage, relevance to neurotoxic and neurodegenerative mechanisms. J Agric Food Chem., 56:5994–6003.
19) **Yu, S., Son, F., Yu, J., Zhao, X., Yu, L., Li, G. and Xie, K. (2006).** Acrylamide alters cytoskeletal protein in sciatic nerve. Neurochem Res., **31**:1197–1204.
20) **Zhu, Y., Zeng, T., Zhu, Y., Yu, S., Wang, Q., Zhang, L., Guo, X. and Xie, K. (2008).** Effects of acrylamide on the nervous tissue antioxidant system and sciatic nerve electrophysiology in the rat. Neurochem Res.**, 33**:2310–2317.
21) **Park, H, Kim, M., Kim, S., Park, M., Kong, K. and Kim, H (2010).** Acrylamide induces cell death in neural progenitor cells and impairs hippocampal neurogenesis. Toxicol Lett, **193**:86–93.
22) **Ahmed, M. M., Farid, O. A. and Shehata. A. M. (2016).** A neuroprotective role for ferulic acid against acrylamide-induced neurotoxicity in rats. Journal of Global Biosciences **5**(2):3635-3644.
23) **Ahmed, M. M and Elmenoufy G. (2016).** Ameliorative Effect of Ferulic Acid on Acrylamide-induced Inflammation and Oxidative Damage in Rat Testes. Research Journal of Pharmaceutical, Biological and Chemical Sciences. **7**(1):396-403.
24) **Dwivedi, N. and Flora, S. J. (2011).** Dose dependent efficacy of quercetin in preventing arsenic induced oxidative stress in rat blood and liver. J. Cell Tissue Res. **11**(1):2605–2611.
25) A**bdel-Daim, M. M., AbdelDaim, M. A. and Hassan, A. G. (2014).** *Trigonella foenum graecum* ameliorates acrylamide-induced toxicity in rats: Roles of oxidative stress, proinflammatory Cytokines, and DNA damage. Biochem Cell Biol., **93**(1):192-198.
26) **Sudhakar, N. S. and Pattabiraman, T. N. (1981).** A new colorimetric method for the estimation of glycosylated haemoglobin. Clin Chem Acta. **109**:267-274.
27) **Friedewald, W. T., Levy, R. I. and Fredrickson, D. S. (1972).** Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem., **18**:499 –502.
28) **Totani, N., Yawata, M., Ojiri, Y. and Fujioka, Y. (2007).** Effects of trace acrylamide intake in Wistar rats. J. Oleo. Sci., **56**(9):501-506.
29) **Tang, Y., Li, Y. and Yu, H. (2014).** Quercetin attenuates chronic ethanol hepatotoxicity: implication of "free" iron uptake and release," Food Chem Toxicol., **67**:131-138.
30) **Seiva, F. R., Chuffa, L. G. and Braga, C. P. (2012.** Quercetin ameliorates glucose and lipid metabolism and improves antioxidant status in postnatal monosodium glutamate-induced metabolic alterations," Food ChemToxicol., **50**(10):3556-3561.
31) **Alam, M. M., Meerza, D. and Naseem, I. (2014).** Protective effect of quercetin on hyperglycemia, oxidative stress and DNA damage in alloxan induced type 2 diabetic 27 mice. Life Sci., **109**(1):8-14.
32) **Mahmood, S. A. F., Amin, K. A. M. and Salih, S. F. M. (2015).** Effect of Acrylamide on Liver and Kidneys in Albino Wistar Rats. Int J Curr Microbiol App Sci., **4**(5):434-444.
33) **Teodor, V., Cuciureanu, M., Slencu, B. G., Zamosteanu, N. and Cuciureanu, R. (2011).** Potential protective role of selenium in acrylamide intoxication. A biochemical study. Studia Universitatis VasileGoldis Seria Stiintele Vietii. Life Sciences Series, **2**:21-26.
34) **Allam, A. A., El-Ghareeb, A. W., Abdul-Hamid M., Bakery, A. E., Gad, M. and Sabri, M. (2010).** Effect of prenatal and perinatal acrylamide on the biochemical and morphological changes in liver of developing albino rat. Arch. Toxicol., **84**(2):129-141.
35) **Rawi, S. M., Marie, M. A. S., Fahmy, S. R. and El-Abied, S. A. (2012).** Hazardous effects of acrylamide on immature male and female rats." Afr J Pharm Pharmacol., **6**(18):1367-1386.
36) **Kamada, C., da Silva, E. L., Ohnishi-Kameyama, M., Moon, J. H. and Terao, J. (2005).** Attenuation of lipid peroxidation and hyperlipidemia by quercetinglucoside in the aorta of high cholesterol-fed rabbit. Free Radic Res, **39**:185–194.
37) **Gnoni, G. V., Paglialonga, G. and Siculella, L. (2009).** Quercetin inhibits fatty acid and triacylglycerol synthesis in rat-liver cells. Eur J Clin Invest, **39:** 761–768.
38) **Lee, K. H., Park, E., Lee, H. J., Kim, M. O., Cha, Y. J., Kim, J. M., Lee, H. and Shin, M. J. (2011).** Effects of daily quercetin-rich supplementation on cardiometabolic risks in male smokers. Nutr Res Pract, **5**:28–33.
39) **Igarashi, K. and Ohmuma, M. (1995).** Effects of isorhamnetin, rhamnetin and quercetin on the concentrations of cholesterol and lipoperoxide in the serum and liver and on the blood and liver antioxidative enzyme activities of rats. Biosci Biotechnol Biochem, **59 (4):** 595-601.
40) **Sharma, A. and Jain, J. (2008).** Effects of oral exposure of acrylamide on plasma levels of thyroid hormones and haematological parameters in the Swiss albino mice, Asian. J. Exp. Sci., **(22):** 317-324.
41) **Rizos C.V, Elisaf M.S, Liberopoulos EN (2011).** Effects of thyroid dysfunction on lipid profile. Open Cardiovasc. Med J. **5:** 76-84.
42) **Peppa, M., Betsi, G. and Dimitriadis, G (2011).** Lipid abnormalities and cardiometabolic risk in patients with overt and subclinical thyroid disease. J Lipids. **2011**:1-9.

43) **Choi, Y. J., Kang, J. S., Park, J. H., Lee, Y. J., Choi, J. S. and Kang, Y. H. (2003).** Polyphenolic flavonoids differ in their antiapoptotic efficacy in hydrogen peroxide–treated human vascular endothelial cells. J Nutr .**133**(4):985-91.

44) **Ferrali, M., Signorini, C., Ciccoli, L., Bambagioni, S., Rossi, V., Pompella, A. and Comporti, M. (2000).** Protection of erythrocytes against oxidative damage and autologous immunoglobulin G (IgG) binding by iron chelator fluor-benzoil-pyridoxal hydrazone. Biochem Pharmacol. **59**(11):1365-1373.

45) **Abd El-Mottaleb, E. M. and Rashed, A. Y. (2008).** Studies on acrylamide intoxication in male albino rats. Egypt J Comp & Clinic Path., **21**(4):222 - 245.

46) **El-Beltagi, H. S. and Ahmad, M. M., (2016).** Assessment the Protective Role of quercetin on acrylamide-induced Oxidative Stress in Rats. J Food Biochem., **40**(6):715–723.

47) **Collodel, G., Moretti, E., Fontani, V., Rinaldi, S., Aravagli, L., Sarago, G., Capitani, S. and Anichini, C. (2008).** Effect of emotional stress on sperm quality. Indian J. Med. Res., **128:**254-261.

48) **Khaki, A., Ouladsahebmadarek, E., Javadi, L., Farzadi, L., Fathiazad, F. and Nouri, M. (2011).** Anti-oxidative effects of citroflavonoids on spermatogenesis in rat. Afric J Pharma. Pharmacol. **5**(6):7215-7221.

49) **Ma, Z., Nguyen, T. H., Huynh, T. H., Do, P. T. and Huynh, H. (2004).** Reduction of rat prostate weight by combined quercetin-finasteride treatment is associated with cell cycle deregulation. J Endocrinol., **181**(3):493-507.

50) **Kaya, K., Ciftci, O., Cetin, A., Doğan, H. and Başak, N. (2015).** Hesperidin protects testicular and spermatological damages induced by cisplatin in rats. Andrologia. **47**(7):793-800.

51) **Nna, V. U., Usman, U. Z., Ofutet, E. O. and Owu, D. U. (2017).** Quercetin exerts preventive, ameliorative and prophylactic effects on cadmium chloride-induced oxidative stress in the uterus and ovaries of female Wistar rats. Food Chem Toxicol., **102:** 143-155.