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Research Article
Therapeutic and Biochemical Effects of Garlic (*Allium sativum*) on Acrylamide Toxicity in Rabbits: Glycolytic Pathway

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Abstract
The stimulation of oxidative stress and lipid peroxidation by acrylamide has been extensively documented. However, the effect of acrylamide on glycolytic enzymes has not been completely elucidated. The present study investigated the effect of acrylamide exposure on activities of serum and hepatic glycolytic enzymes namely, pyruvate kinase, glyceraldhyde-3-phoshate dehydrogenase, phosphofructokinase, hexokinase and α-glucosidase in rabbits. In addition, the protective effect of garlic (*Allium sativum*) against acrylamide toxicity as reflected on glycolytic enzyme activities has been estimated. Rabbits were exposed to acrylamide dissolved at a concentration of 0.03% (w/v, corresponding to 4.2 mM acrylamide) in distilled water with or without diet containing 1.5% of garlic powder for 42 days. Acrylamide administration reduced the activities of all investigated glycolytic enzymes in serum and liver tissues of rabbits. However, administration of garlic powder with acrylamide significantly attenuated the reduction of activities of these enzymes. In conclusion, the present study emphasized the role of garlic as a potential adjuvant therapy to attenuate acrylamide toxicity in rabbits.

Key words: Acrylamide, garlic, glycolytic enzymes, serum, liver, rabbits

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Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Acrylamide is a water-soluble vinyl monomer used for polyacrylamide synthesis. Acrylamide formed through the Maillard reaction from amino acids and reducing sugars during drying and baking (Mottram *et al*., 2002). Therefore, starchy foods that have been heated at high temperature produced a huge amount of acrylamide (Tareke *et al*., 2002). After absorption, acrylamide interacts with nucleophiles possessing -SH, -OH or -NH_2 transformed via glutathione conjugation and decarboxylation (Brantsaeter *et al*., 2008), metabolized by cytochrome P2E1 forming genotoxic epoxide glycidamide (Sumner *et al*., 1999) and finally excreted in the urine (Bjellaas *et al*., 2005). It is a neurotoxin for both central and peripheral systems (Sickles *et al*., 2002). The toxicity was in the form of ataxia, skeletal muscle weakness and weight loss (Le Quesne, 1985; Spencer and Schaumburg, 1974). Acrylamide toxicity is mainly neurotoxicity in human whereas carcinogenicity and reproductive toxicity was reported in laboratory animals (Li *et al*., 2006). The mechanisms of neurotoxicity remain controversial. Several studies demonstrated the effect of acrylamide on stimulation of oxidative stress in rats (Srivastava *et al*., 1986; Awad *et al*., 1998; Mohamed *et al*., 2013; Taha *et al*., 2013). Moreover, acrylamide may produce its neurotoxicity via glycolytic enzymes inhibition with subsequent alteration in lipid metabolism (Sakamoto and Hashimoto, 1985a, b).

Discovery of effective natural product, which able to attenuates or detoxifies the environmental toxicants is an important scientific issue. Garlic (*Allium sativum* L.), is a famous spice of anticancer, antidiabetic, antioxidant and immune modulation activities (Razo-Rodriguez *et al*., 2008; Chihara *et al*., 2010; Abd El-Halim and Mohamed, 2012; Taha *et al*., 2013). The major beneficial effects of garlic were attributed to the high content of organosulfur compounds produced when the garlic tissue is crushed and the odorless precursors are converted by the alliinase enzyme (Vazquez-Prieto and Miatello, 2010). Alliinase enzyme acts on alliin (S-allylcysteine sulfoxide) to produce antioxidant compound named allicin (Lawson and Wang, 2005), which able to scavenging hydroxyl radicals and inhibiting lipid peroxidation (Pedraza-Chaverri *et al*., 2006). In addition, garlic components were able to increase the activities of antioxidant enzymes such ad catalase, superoxide dismutase, glutathione peroxidase and glutathione-s-transferase (Xie *et al*., 2008; Ghareeb *et al*., 2010; Taha *et al*., 2013). In addition, the inhibition of cytochrome P2E1 and consequently prevention of oxidative biotransformation of acrylamide to carcinogenic glycidamide by garlic component, diallyl trisulfide has been reported (Taubert *et al*., 2006). In the current study, acrylamide dissolved in distilled water at a concentration of 0.03% was administered with or without 1.5% of garlic (*Allium sativum*) powder for 42 days to evaluate the protective effect of garlic against acrylamide toxicity based on evaluation of glycolytic enzyme activities in serum and liver tissues of rabbits.

MATERIALS AND METHODS

Chemicals, kits and plant: Routine chemicals and solvents used in the study were of highest grade and commercially available. Acrylamide (99.9%) was purchased from Sigma Chemical Company (St. Louis, MO, USA). Acrylamide was dissolved at a concentration of 0.03% (w/v, corresponding to 4.2 mM acrylamide) in distilled water for rabbits administration (Ghareeb *et al*., 2010). Acrylamide solution was changed frequently at 7 day intervals along an experimental period of 42 days. Garlic (*Allium sativum*) was purchased from local market at Al-Ahsa, Saudi Arabia. The outer husks of garlic were peeled off and then the cloves were sliced and dried at 60°C up to dryness. The dried garlic slices were ground and kept dry in sealed plastic package until used (Mohamed-Yasseen *et al*., 1994). Garlic powder was mixed into the powdered basal diet at concentration of 1.5% (Ghareeb *et al*., 2010). Commercial kits for pyruvate kinase, glyceraldhyde-3-phoshate dehydrogenase, phosphofructokinase, hexokinase and α-glucosidase were bought from Biodiagnostic Company (Cairo, Egypt).

Animals and treatment: Animal experiment was performed according to the Guide for the Care and Use of Laboratory Animals, National Institutes of Health (ILAR., 1996) and approved by the King Faisal University Animal Care and Use Committee (KFU-ACUC). A total of 20 male rabbits (2 months old, 600-1000 g) were obtained from Laboratory House, College of Veterinary Medicine and Animal Resources, King Faisal University, Saudi Arabia. Rabbits were maintained at metal cages and received diet and water *ad libitum* for two weeks before the start experiment for acclimatization and to ensure the normal growth and behavior. The animals were divided into 4 equal groups. Group I, rabbits were fed on basal diet and fresh water and served as untreated control; Group 2, rabbits were fed on supplemented basal diet with 1.5% garlic powder (Ghareeb *et al*., 2010); Group 3, rabbits were fed on basal diet and acrylamide solution and Group 4, rabbits were fed on supplemented basal diet with 1.5% garlic powder and

acrylamide solution. Acrylamide solution was administered once daily via esophageal gavages (3.33 mL kg^{-1} b.wt.) (Ghareeb *et al*., 2010).

Samples collection: After 42 days, rabbits were anaesthetized by diethyl ether and the blood was collected form ear vein as well as the liver were quickly removed and placed in phosphate buffer (pH 7.4). The tissues were freed from adhering blood by repeated washing with the same buffer. The harvested serum and hepatic tissues stored frozen at -20°C until the time of analysis of activities of glycolytic enzymes.

Biochemical analysis: Commercial diagnostic kits (Sigma-Aldrich Chemie GmbH, Germany) were used for determination of pyruvate kinase (Cat#MAK072), glyceraldhyde-3-phoshate dehydrogenase (Cat#MAK208), phosphofructokinase (Cat#MAK093), hexokinase (Cat#MAK091) and α-glucosidase (Cat#MAK123) by ELISA reader (Absorbance Microplate Reader ELx 800TM BioTek®, USA). Results were calculated according to the manufacture instructions.

Statistical analysis: Data are expressed as the Mean±SD (Standard Deviation). One way analysis of variance (ANOVA) followed by LSD's *post hoc* tests, which was provided by SPSS program. The differences were considered statistically significant at $p \leq 0.05$.

RESULTS

The effects of acrylamide and/or garlic on serum glycolytic enzymes of rabbits are presented in Table 1. The data indicated that garlic administered alone (group 2) did not affect the activities of pyruvate kinase (1.23±0.02 μmol mL^{-1} min^{-1}), glyceraldehyde-3-phosphate dehydrogenase (1.73±0.03 μmol mL^{-1} min^{-1}), Phosphofructokinase (2.41±0.01 μmol mL^{-1} min^{-1}), Hexokinase (1.15±0.01 μmol mL^{-1} min^{-1}) and α-glucosidase (189±8.00 μmol mL^{-1} h^{-1}) in the serum of rabbits and remained comparable to values of control, group1 (1.20±0.05 μmol mL^{-1} min^{-1}, 1.65±0.04 μmol mL^{-1} min^{-1}, 2.36±0.01 μmol mL^{-1} min^{-1}, 1.05±0.01μmol m^{-1} min^{-1} and 179±5.00 μmol mL^{-1} h^{-1}), respectively. Acrylamide (group 3) reduced the activities of these enzymes respectively (0.47±0.02 μmol mL^{-1} min^{-1}, 0.29±0.01 μmol $mL^{-1}min^{-1}$, 1.14±0.01 μmol mL^{-1} min^{-1}, 0.52±0.01 μmol mL^{-1} min^{-1} and 31±10.00 μmol mL^{-1} h^{-1}), in serum of rabbits compared to group 1 and group 2. Co-administration of garlic with acrylamide solution (group 4) to rabbits attenuated the detrimental effect of acrylamide on activities of these glycolytic enzymes in serum, respectively (0.89±0.01 μmol mL^{-1} min^{-1}, 0.94±0.01 μmol mL^{-1} min^{-1}, 1.95±0.01 μmol $mL^{-1}min^{-1}$, 0.80±0.01 μmol ml^{-1} min^{-1} and 139±12.00 μmol mL^{-1} h^{-1}) compare to acrylamide treated group (group 3) but still lower than that of controls (group 1 and 2).

Data summarized in Table 2 showed the effects of acrylamide and/or garlic on hepatic glycolytic enzymes of rabbits. The data indicated that, administration of garlic alone (group 2) did not affect the activities of pyruvate kinase (0.71±0.02 μmol g^{-1} min^{-1}), glyceraldehyde-3-phosphate dehydrogenase (1.07±0.03 μmol g^{-1} min^{-1}), phosphofructokinase (5.41±0.02 μmol g^{-1} min^{-1}), hexokinase (3.06±0.02 μmol $g^{-1}min^{-1}$) and α-glucosidase (4778±15.00 μmol $g^{-1}h^{-1}$) in liver tissues of rabbits and remained comparable to values of control, group 1 (0.72±0.01 μmol g^{-1} min^{-1}, 1.1±0.02 μmol $g^{-1}min^{-1}$, 4.94±0.03 μmol g^{-1} min^{-1}, 2.91±0.14 μmol g^{-1} min^{-1} and 4740±20.00 μmol $g^{-1}h^{-1}$), respectively. Acrylamide (group 3) reduced the activities of these enzymes respectively (0.11±0.03 μmol g^{-1} min^{-1}, 0.13±0.01 μmol g^{-1} min^{-1}, 1.87±0.01 μmol g^{-1} min^{-1},1.17±0.03 μmol g^{-1} min^{-1} and 598.9±12.00 μmol g^{-1} h^{-1}) in the liver tissues of rabbits compared to controls (group 1 and 2). Co-administration of

Table 1: The effect of acrylamide and/or garlic on serum glycolytic enzymes

	Groups			
Parameters	1	2	3	4
Pyruvate kinase (μmol mL^{-1} min^{-1})	1.20±0.05	1.23 ±0.02	0.47±0.02*	0.89±0.01**
Glyceraldehyde-3-phosphate dehydrogenase (μmol mL^{-1} min^{-1})	1.65±0.04	1.73±0.03	0.29±0.01*	0.94±0.01**
Phosphofructokinase (μmol mL^{-1} min^{-1})	2.36±0.01	2.41±0.01	1.14±0.01*	1.95±0.01**
Hexokinase (μmol mL^{-1} min^{-1})	1.05±0.01	1.15±0.01	0.52±0.01*	0.80±0.01**
α-glucosidase (μmol mL^{-1} h^{-1})	179±5.00	189±8.00	31±10.00*	139±12.00**

*Mean values are significantly ($p<0.05$) different compare to the control (group 1), **Mean values are significantly ($p<0.05$) different compare to acrylamide treated rabbits (group 3), Group 1: Rabbits were fed on basal diet and fresh water and served as untreated control, Group 2: Rabbits were fed on supplemented basal diet with 1.5% garlic powder, Group 3: Rabbits were fed on basal diet and acrylamide solution, Group 4: Rabbits were fed on supplemented basal diet with 1.5% garlic powder and acrylamide solution

Table 2: The effect of acrylamide and/or garlic on hepatic glycolytic enzymes

	Groups			
Parameters	1	2	3	4
Pyruvate kinase (μmol g^{-1} min^{-1})	0.72±0.01	0.71±0.02	0.11±0.03*	0.32±0.01**
Glyceraldehyde-3-phosphate dehydrogenase (μmol g^{-1} min^{-1})	1.1±0.02	1.07±0.03	0.13±0.01*	0.54±0.02**
phosphofructokinase (μmol g^{-1} min^{-1})	4.94±0.03	5.41±0.02	1.87±0.01*	2.95±0.04**
Hexokinase (μmol g^{-1} min^{-1})	2.91±0.14	3.06±0.02	1.17±0.03*	2.08±0.01**
α Glucosidase (μmol g^{-1} h^{-1})	4740±20.00	4778±15.00	598.9±12.00*	2224±17.00**

*Mean values are significantly ($p<0.05$) different compare to the control (group 1), **Mean values are significantly ($p<0.05$) different compare to acrylamide treated rabbits (group 3), Group 1: Rabbits were fed on basal diet and fresh water and served as untreated control, Group 2: Rabbits were fed on supplemented basal diet with 1.5% garlic powder, Group 3: Rabbits were fed on basal diet and acrylamide solution, Group 4: Rabbits were fed on supplemented basal diet with 1.5% garlic powder and acrylamide solution

garlic with acrylamide solution (group 4) to rabbits attenuated the detrimental effect of acrylamide on these glycolytic enzymes respectively in the liver tissues (0.32±0.01 μmol g^{-1} min^{-1}, 0.54±0.02 μmol g^{-1} min^{-1}, 2.95±0.04 μmol g^{-1} min^{-1}, 2.08±0.01 μmol g^{-1} min^{-1} and 2224±17.00 μmol g^{-1} h^{-1}) compare to acrylamide treated group (group 3) but still lower than that of controls (group1 and 2).

DISCUSSION

To the best of authors knowledge, this is the first study to address the effect of acrylamide and/or garlic on the activities of glycolytic enzymes in rabbits. In the present study, acrylamide reduced the activities of examined glycolytic enzymes in serum and hepatic tissue of rabbits. This finding confirmed the hepatotoxicity effect of acrylamide as reported previously (Ghareeb *et al*., 2010; Ghorbel *et al*., 2015). Parallel to the current findings, acrylamide inhibited the activities of glycolytic enzymes namely, glyceraldhyde-3-phoshate dehydrogenase and enolase in sciatic nerve tissues of rats and induced neurotoxicity *in vitro* (Sakamoto and Hashimoto, 1985b) and *in vivo* (Sakamoto and Hashimoto, 1984; Sakamoto and Hashimoto, 1985a; Tanii and Hashimoto, 1984). In another study (Tanii and Hashimoto, 1983), acrylamide inhibited the activities of glyceraldhyde-3-phoshate dehydrogenase and phosphofructokinase whereas, the activities of rate-limiting enzymes in glycolysis, hexokinase and pyruvate kinase were not inhibited at all. Glyceraldhyde-3-phoshate dehydrogenase and phosphofructokinase in nervous tissues have been inhibited by acrylamide *in vivo* and *in vitro* (Howland *et al*., 1980; Howland, 1981). The inhibition has been postulated as being involved in the neurotoxic mechanism of acrylamide-induced neuropathy. Glycolytic enzymes are enzymes catalyze the oxidation of glucose into pyruvic acid in a cycle named glycolysis. These enzymes are α-glucosidase, hexokinase, phosphofructokinase, glyceraldhyd e-3-phoshate dehydrogenas a pyruvate kinase. Alpha glucosidaselocated at the brush border of the small intestine acts on 1,4-α bonds and breakdowns starch and disaccharides into glucose. Hexokinase phosphorylated the absorbed glucose into glucose-6-phosphat, whereas phosphofructokinase phosphorylates fructose-6-phosphate into 1,6-bisfructophosphate. Glyceraldhyde-3-phoshate dehydrogenase catalyze the oxidation of glyceraldhyde-3-phosphate into glycerate 1,3-bisphosphate. Pyruvate kinase catalyzes the transfer of a phosphate group from phosphoenolpyruvate to adenosine diphosphate, yielding one molecule of pyruvate and adenosine triphosphate. All cascades of the reactions aimed to complete oxidation of glucose for fuel production. If these glycolytic enzymes are inhibited, the energy production of glucose oxidation will be stopped accordingly and the energy metabolism could be shifted into risky lipid mobilization and oxidation of free fatty acids. The significant increase in glycolytic enzymes activities in rabbits intoxicated with acrylamide and treated with garlic indicated protective effect of garlic against acrylamide induced liver toxicity (Ghareeb *et al*., 2010; Mohamed *et al*., 2013; Taha *et al*., 2013). The protective effect of garlic was documented against and cisplatin induced renal changes (Nasr and Saleh, 2014). All previous studies by Ghareeb *et al*. (2010), Mohamed *et al*. (2013), Taha *et al*. (2013) and Nasr and Saleh (2014) demonstrated that, garlic protects liver and/or renal tissues against toxicity via stimulation of enzymatic and non-enzymatic antioxidants. However, the current study demonstrated that, acrylamide induced its toxicity by reduction of glycolytic enzymes and garlic reactivates these activities again. The mode of action of inhibition and activation of glycolytic enzymes by acrylamide or garlic respectively was beyond the objective of the present study. Therefore, large scale studies are recommended to determine the mode of action of both acrylamide and garlic on inhibition and activation of glycolytic enzymes, respectively.

CONCLUSION

Acrylamide administration reduced the activities of glycolytic enzymes namely pyruvate kinase, glyceraldhyde-3-

phoshate dehydrogenase, phosphofructokinase, hexokinase and α-glucosidase in serum and liver tissues of rabbits. Administration of garlic powder with acrylamide significantly attenuated the reduction of activities of these enzymes. The current study emphasized the role of garlic as a potential adjuvant therapy to attenuate acrylamide toxicity in rabbits.

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