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Biochemical study on the hypoglycemic effects of onion and garlic in alloxan-induced diabetic rats

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Abstract

The present study was carried out to investigate the effects of onion (*Allium cepa* Linn) and garlic (*Allium sativum* Linn) juices on biochemical parameters, enzyme activities and lipid peroxidation in alloxan-induced diabetic rats. Alloxan was administered as a single dose (120 mg/kg BW) to induce diabetes. A dose of 1 ml of either onion or garlic juices/100 g body weight (equivalent to 0.4 g/100 g BW) was orally administered daily to alloxan-diabetic rats for four weeks. The levels of glucose, urea, creatinine and bilirubin were significantly ($p < 0.05$) increased in plasma of alloxan-diabetic rats compared to the control group. Aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), and alkaline and acid phosphatases (AlP, AcP) activities were significantly ($p < 0.05$) increased in plasma and testes of alloxan-diabetic rats, while these activities were decreased in liver compared with the control group. Brain LDH was significantly ($p < 0.05$) increased. The concentration of thiobarbituric acid reactive substances and the activity of glutathione S-transferase in plasma, liver, testes, brain, and kidney were increased in alloxan-diabetic rats. Treatment of the diabetic rats with repeated doses of either garlic or onion juices could restore the changes of the above parameters to their normal levels. The present results showed that garlic and onion juices exerted antioxidant and antihyperglycemic effects and consequently may alleviate liver and renal damage caused by alloxan-induced diabetes.

Keywords: Rats; Alloxan; Onion; Garlic; Biochemical parameters; Enzymes; Lipid peroxidation

1. Introduction

Dietary factors play a key role in the development of various human diseases, including cardiovascular and other metabolic diseases, atherosclerosis, hyperlipidemia thrombosis, hypertension and diabetes (Banerjee and Maulik, 2002). Medicinal plants continue to provide valuable therapeutic agents, in both modern medicine and in traditional system. The doubts about the efficacy and safety of the oral hypoglycemic agents have prompted a search for safer and more effective drugs in the treatment of diabetes (Reaven et al., 1983). In spite of the fact that insulin has become one of the most important therapeutic agents known to medicine, researchers have been making efforts to find insulin substitutes from synthetic or plant sources for the treatment of diabetes. Many herbs have remained as an alternative to conventional therapy especially in poor areas where insulin is not readily available (Sanchez et al., 1994).

Allium species such as onions and garlic are used as foodstuff, condiment, flavoring, and folk medicine. Garlic has attracted particular attention of modern medicine because of its widespread health use around the world, and the cherished belief that it helps in maintaining good health, warding off illnesses and providing more

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vigor. The biological responses of garlic have been largely attributed to (i) reduction of risk factors for cardiovascular diseases and cancer, (ii) stimulation of immune function, (iii) enhanced detoxification of foreign compound, (iv) hepatoprotection, (v) antimicrobial effect and (vi) antioxidant effect (Banerjee and Maulik, 2002). Onion was also a popular folk remedy. It is rich in flavonoids such as quercetin and sulfur compounds, such as allyl propyl disulphide that have perceived benefits to human health (Griffiths et al., 2002). In addition, onion and garlic are rich in sulfur containing compounds mainly in the form of cysteine derivatives, viz. S-alkyl cysteine sulfoxides which are decomposed the enzyme allinase into a variety of volatile compounds such as thiosulfinates and polysulfides during extraction. These compounds possess antidiabetic, antibiotic, hypocholesterolaemic, fibrinolytic, and various other biological effects. In addition to volatile substances in alliums, there are nonvolatile sulfur-containing peptides and proteins which have been shown to have potential health benefits (Augusti, 1996). Therefore, the purpose of the present study was to examine the influence of oral administration of either onion or garlic on the levels of free radicals, biochemical parameters, and the activities of some enzymes in plasma and different tissues of alloxan-induced diabetic rats.

2. Materials and methods

2.1. Animals and treatments

Fresh onion (*Allium cepa* Linn) and garlic (*Allium sativum* Linn) bulbs were obtained from the local market in Alexandria, Egypt and cut into small pieces. About 250 ml of distilled water per 100 g of onion and/or garlic were added and crushed in a mixing machine. The resultant slurry was squeezed and filtered through a fine cloth and the filtrate was quickly frozen until used. Alloxan (hydrate) LR, $C_4H_2N_2O_4 \cdot H_2O$, was purchased from S.d.Fine-Chem Ltd., Boisar 401 506. Alloxan was dissolved in saline solution (0.9% sodium chloride, pH 7). The dose of alloxan used was 120 mg/kg BW as a single dose. This dose was chosen because it was effective to induce diabetic as we found from our previous studies (Mansour et al., 2002; Sheweita et al., 2002).

Twenty-eight adult male Sprague–Dawely rats (240–300 g) were obtained from the animal house of the Faculty of Agriculture, Alexandria University, Alexandria, Egypt. The local committee approved the design of the experiments, and the protocol conforms to the guidelines of the National Institutes of Health (NIH). The rats were housed in standard cages where food and water were provided ad libitum. Rats were fed pellets consisted of 30% berseem (*Trifolium alexandrinum*) hay, 25% yellow corn, 26.2% wheat bran, 14% soybean meal, 3% molasses, 1% $CaCl_2$, 0.4% NaCl, 0.3% mixture of minerals and vitamins (0.01 g/kg diet of vitamin E), and 0.1% methionine. The chemical analysis of the pellets (AOAC, 1990) showed that they contained 17.5% crude protein, 14.0% crude fiber, 2.7% crude fat and 2200 K cal./kg diet.

After two weeks of acclimation, animals were divided into two groups. The first group (7 rats) was used as control and received double distilled water as vehicle. The second group (21 rats) was injected subcutaniously (s.c.) with a single dose of alloxan (120 mg/kg BW), and divided into three subgroups (7 rats per each) after stabilization of diabetes for one week. The first subgroup was kept as diabetic. The second subgroup received 1 ml onion juice/100 g BW/day and the third subgroup received 1 ml garlic juice/100 g BW/day by gavage for four weeks. Prior to administration of alloxan, the animals were fasted for 12 h with free access drinking water.

2.2. Enzyme assessments

At the end of the experimental period, rats were fasted for 12 h, and then sacrificed by cervical decapitation and fasting blood samples were collected from the sacrificed animals in tubes with heparin. Plasma samples were obtained by centrifugation at 860*g* for 20 min and stored at −20 °C till measurements. Also, liver, testes, kidney, and brain were immediately removed, weighed and washed using chilled saline solution. Tissues were minced and homogenized (10% w/v), separately, in ice-cold 1.15% KCl–0.01 M sodium, potassium phosphate buffer (pH 7.4) in a Potter–Elvehjem type homogenizer. The homogenate was centrifuged at 10,000*g* for 20 min at 4 °C, and the resultant supernatant was used for different enzyme assays. Plasma, liver and testes alanine aminotransferase (ALT; EC 2.6.1.2) and aspartate aminotransferase (AST; EC 2.6.1.1) activities were assayed by the method of Reitman and Frankel (1957). Plasma, brain, liver and testes lactate dehydrogenase (LDH, EC 1.1.1.27) activity was determined by the method of Cabaud and Wroblewski (1958). Alkaline phosphatase (AlP; EC 3.1.3.1) activity was measured at 405 nm by the formation of paranitrophenol from *para*-nitrophenylphosphate as a substrate (Principato et al., 1985). Acid phosphatase (AcP; EC 3.1.3.2) activity was measured using the method of Moss (1984). Plasma, liver, brain, testes and kidney glutathione S-transferase (GST; EC 2.5.1.18) activity was determined according to Habig et al. (1974), using *para*-nitrobenzylchloride as a substrate. Thiobarbituric acid-reactive substances (TBARS) were measured in plasma, liver, brain, testes and kidney by using the method of Tappel and Zalkin (1959). Protein concentration in liver, testes, brain and kidney supernatants was assayed by the method of Lowry et al. (1951) using bovine serum albumin as a standard.

2.3. Biochemical assays

Stored plasma samples were analyzed for glucose level by using the method of Trinder (1969). Plasma urea, creatinine and total bilirubin concentrations were determined by the methods of Patton and Crouch (1977); Henry et al. (1974) and Pearlman and Lee (1974), respectively. Plasma total bilirubin was measured using the method of Pearlman and Lee (1974).

2.4. Statistical analysis

Data were analyzed as a completely randomized design (Steel and Torrie, 1981) using the General Linear Model procedure of SAS (1986). Means were statistically compared using least significant difference (LSD) test at 0.05 significant level (Steel and Torrie, 1981). The following model was used:

$$Yijk = \mu + ai + bj + abij + eijk$$

where $Yijk$ = experimental observation; μ = overall mean; ai = treatment effect; bj = week effect; $abij$ = interaction effect of treatment and week; $eijk$ = random error.

3. Results

The effects of oral administration of onion and garlic juices on plasma glucose, urea, creatinine and total bilirubin are presented in Table 1. The experimentally induced-diabetes increased ($p < 0.05$) the level of plasma glucose by 199% of control level (Table 1). However, treatment of alloxan-diabetic rats with the juices of onion and garlic reduced their plasma glucose levels by 70% and 68%, respectively compared with the diabetic group.

In alloxan-diabetic rats the activities of plasma AST, ALT, LDH, AlP and Acp were significantly ($p < 0.05$) increased by 49, 60, 37, 51 and 58%, respectively, relative to their normal levels (Table 2). In contrast, the activities of AST, ALT, LDH, AlP and AcP were significantly ($p < 0.05$) decreased in the liver tissue of alloxan-diabetic rats (Table 3) by 47%, 38%, 41%, 35% and 36%, respectively and increased in testes by 38%, 32%, 35%, 31% and 33%, respectively compared to the control values (Table 4). Also, brain LDH activity was significantly ($p < 0.05$) increased by 58% in alloxan-diabetic rats (Table 5).

The present study showed that the levels of free radicals were significantly ($p < 0.05$) increased in plasma, liver, testes, brain and kidney by 28%, 16%, 22%, 38% and 22%, respectively in alloxan-diabetic rats as compared to control values (Tables 2–5). While, after treatment of alloxan-diabetic rats with onion and garlic, the level of free radicals was significantly ($p < 0.05$) decreased in plasma and tissues as compared with the mean value of diabetic group (Tables 2–5).

In the present study the activity of GST was significantly ($p < 0.05$) increased in liver, testes and kidney of both diabetic and, onion and garlic-treated diabetic rats compared with the control values (Tables 3–5).

4. Discussion

The results of plasma glucose, urea, creatinine and total bilirubin (Table 1) are consistent with the finding of Augusti and Sheela (1996) and Campos et al. (2003) in rats, Kumar and Reddy (1999) in mice and Jain and Vyas (1975) in rabbits. Tjokroprawiro et al. (1983) found a significant decrease in blood sugar level in the onion treated diabetic patients. Orekhov and Grunwald (1997) found that garlic indirectly affects atherosclerosis by reduction of hyperlipidemia, hypertension, and probably diabetes mellitus and prevents thrombus formation.

Augusti and Sheela (1996) reported that garlic acts as an insulin secretagogue in diabetic rats. Another proposed mechanism is due to spare insulin from sulfhydryl group. Inactivation of insulin by sulfhydryl group is a common phenomenon. Garlic can effectively combine with compounds like cysteine and enhance serum insulin (Mathew and Augusti, 1973). Jain and Vyas (1975) proposed that garlic can act as an antidiabetic agent by increasing either the pancreatic secretion of insulin from the beta cells or its release from bound insulin. Kumari and Augusti (2002) reported that S-methylcysteine sulfoxide (SMCS), isolated from onion, had antihyperglycemic and antioxidant effect. The probable mechanism of

Table 1
Plasma glucose, urea, creatinine and bilirubin levels in control, diabetic, and diabetic treated male rats with onion (O) and garlic (G) (Means ± SE)

Parameters (mg/dl)	Experimental groups			
	Control	Diabetic	Diabetic + O	Diabetic + G
Glucose	96 ± 5.64[b]	287 ± 7.20[a]	85 ± 6.10[b]	91 ± 4.86[b]
Urea	35 ± 2.50[b]	49 ± 2.67[a]	41 ± 2.31[ab]	42 ± 1.58[ab]
Creatinine	0.55 ± 0.018[b]	0.93 ± 0.14[a]	0.63 ± 0.075[b]	0.69 ± 0.023[ab]
Bilirubin	0.73 ± 0.070[b]	1.14 ± 0.083[a]	0.82 ± 0.034[b]	0.86 ± 0.098[b]

Values are the means of seven rats.
[ab]Within rows, between control and treated animals, means with different superscript letters differ significantly ($P < 0.05$).

Table 2
Assay of plasma enzyme activities and thiobarbituric acid-reactive substances (TBARS) in control, diabetic, and diabetic treated male rats with onion (O) and garlic (G) (Means ± SE)

Parameter	Experimental groups			
	Control	Diabetic	Diabetic + O	Diabetic + G
AST (U/dl)	40 ± 1.02^{c}	60 ± 2.34^{a}	45 ± 2.95^{bc}	52 ± 0.94^{b}
ALT (U/dl)	51 ± 2.07^{c}	82 ± 4.37^{a}	60 ± 5.96^{bc}	67 ± 2.78^{b}
LDH (U/l)	1074 ± 92^{b}	1474 ± 54^{a}	1263 ± 68^{ab}	1305 ± 43^{a}
AlP (U/l)	48 ± 3.03^{c}	73 ± 3.40^{a}	59 ± 2.70^{b}	66 ± 2.67^{ab}
AcP (U/l)	11.3 ± 0.78^{c}	17.8 ± 0.68^{a}	13.7 ± 0.81^{b}	14.1 ± 0.28^{b}
GST (μmol/h)	0.54 ± 0.015^{a}	0.52 ± 0.009^{a}	0.56 ± 0.028^{a}	0.52 ± 0.011^{a}
TBARS (nmol/ml)	0.65 ± 0.06^{b}	0.83 ± 0.05^{a}	0.70 ± 0.05^{a}	0.73 ± 0.06^{a}

Values are the means of seven rats.
^{abc}Within rows, between control and treated animals, means with different superscript letters differ significantly ($P < 0.05$).

Table 3
Assay of liver enzyme activities and thiobarbituric acid-reactive substances (TBARS) in control, diabetic, and diabetic treated male rats with onion (O) and garlic (G) (Means ± SE)

Parameter	Experimental groups			
	Control	Diabetic	Diabetic + O	Diabetic + G
AST*	127 ± 3.35^{a}	67 ± 3.24^{c}	106 ± 2.13^{b}	98 ± 2.36^{b}
ALT*	123 ± 5.74^{a}	76 ± 3.38^{c}	101 ± 5.99^{b}	107 ± 7.33^{ab}
LDH**	2246 ± 176^{a}	1336 ± 61^{c}	1829 ± 92^{b}	1745 ± 150^{b}
AlP*	338 ± 23.0^{a}	219 ± 7.6^{c}	294 ± 10.2^{ab}	265 ± 18.1^{bc}
AcP*	16.1 ± 1.20^{a}	10.3 ± 0.71^{c}	13.5 ± 0.97^{ab}	12.3 ± 0.35^{bc}
GST***	0.80 ± 0.052^{c}	1.35 ± 0.059^{a}	1.15 ± 0.049^{b}	1.17 ± 0.008^{b}
TBARS****	26.4 ± 1.14^{b}	30.6 ± 1.10^{a}	26.1 ± 0.50^{b}	28.3 ± 1.07^{b}

Values are the means of seven rats.
^{abc}Within rows, between control and treated animals, means with different superscript letters differ significantly ($P < 0.05$).
* IU/mg: international unit, the amount of the enzyme that under defined assay conditions will catalyze 1 mole of substrate per minute, per mg protein.
** IU/g: international unit, the amount of the enzyme that under defined assay conditions will catalyze 1 mole of substrate per minute, per gram tissue.
*** GST specific activity: μmol/h/mg protein.
**** TBARS is expressed as nmol/g tissue.

Table 4
Assay of testes enzyme activities and thiobarbituric acid-reactive substances (TBARS) in control, diabetic, and diabetic treated male rats with onion (O) and garlic (G) (Means ± SE)

Parameter	Experimental groups			
	Control	Diabetic	Diabetic + O	Diabetic + G
AST*	94 ± 5.52^{c}	129 ± 6.38^{a}	106 ± 4.54^{bc}	112 ± 3.00^{b}
ALT*	81 ± 5.95^{b}	107 ± 3.76^{a}	91 ± 5.12^{ab}	90 ± 5.16^{ab}
LDH**	1060 ± 82^{b}	1430 ± 67^{a}	1222 ± 62^{ab}	1315 ± 77^{a}
AlP*	486 ± 19^{b}	635 ± 22^{a}	557 ± 67^{ab}	542 ± 34^{ab}
AcP*	11.1 ± 0.44^{b}	14.7 ± 1.01^{a}	12.3 ± 0.56^{b}	13.2 ± 0.51^{ab}
GST***	0.78 ± 0.01^{b}	1.07 ± 0.01^{a}	0.97 ± 0.06^{a}	1.03 ± 0.04^{a}
TBARS****	16.5 ± 0.39^{c}	20.1 ± 0.76^{a}	17.8 ± 0.45^{bc}	18.7 ± 0.74^{ab}

Values are the means of seven rats.
^{abc}Within rows, between control and treated animals, means with different superscript letters differ significantly ($P < 0.05$).
* IU/mg: international unit, the amount of the enzyme that under defined assay conditions will catalyze 1 mole of substrate per minute, per mg protein.
** IU/g: international unit, the amount of the enzyme that under defined assay conditions will catalyze 1 mole of substrate per minute, per gram tissue.
*** GST specific activity: μmol/h/mg protein.
**** TBARS is expressed as nmol/g tissue.

Table 5
Assay of brain and kidney enzyme activities and thiobarbituric acid-reactive substances (TBARS) in control, diabetic, and diabetic treated male rats with onion (O) and garlic (G) (Means ± SE)

Parameter	Experimental groups			
	Control	Diabetic	Diabetic + O	Diabetic + G
Brain				
LDH*	1254 ± 54[c]	1982 ± 84[a]	1571 ± 55[b]	1729 ± 59[b]
GST**	0.42 ± 0.001[a]	0.42 ± 0.004[a]	0.43 ± 0.006[a]	0.43 ± 0.006[a]
TBARS***	25.7 ± 0.80[c]	35.4 ± 1.04[a]	28.5 ± 0.80[b]	29.5 ± 1.44[b]
Kidney				
GST**	0.75 ± 0.027[b]	1.08 ± 0.047[a]	1.02 ± 0.069[a]	1.04 ± 0.068[a]
TBARS***	22.7 ± 0.55[b]	27.6 ± 0.86[a]	26.0 ± 0.82[a]	26.7 ± 0.49[a]

Values are the means of seven rats.
[abc]Within rows, between control and treated animals, means with different superscript letters differ significantly ($P < 0.05$).
* IU/g: international unit, the amount of the enzyme that under defined assay conditions will catalyze 1 mole of substrate per minute, per gram tissue.
** GST specific activity: μmol/h/mg protein.
*** TBARS is expressed as nmol/g tissue.

action of SMCS may be partly due to the stimulation of insulin secretion.

The diabetic hyperglycemia induces elevation of plasma levels of urea and creatinine which are considered as significant markers of renal dysfunction (Almdal and Vilstrup, 1988). The results in Table 1 showed significant ($p < 0.05$) increase in the level of plasma urea and creatinine in the diabetic groups by 40% and 68% of control level, respectively. These results indicated that diabetes could be lead to renal dysfunction. While, after treatment of alloxan-diabetic rats with onion and garlic, the level of urea was significantly ($p < 0.05$) decreased in plasma by 16% and 14%, respectively compared to the mean value of diabetic group (Table 1). Similarly, the elevation of creatinine level caused by diabetes was declined after administration of onion and garlic by 32% and 26% ($p < 0.05$), respectively compared with the diabetic group (Table 1). These results are in agreement with other previous studies on onion (Babu and Srinivasan, 1999), root extract of panax ginseng (Badr El-Din, 1997) and herbal formulation D-400 (Dubey et al., 1994).

The increase in the activities of plasma AST, ALT, LDH, AlP and Acp (Table 2) indicated that diabetes may be induced hepatic dysfunction. Supporting our finding it has been found by Larcan et al. (1979) that liver was necrotized in diabetic patients. Therefore, the increment of the activities of AST, ALT, LDH, AlP and AcP in plasma may be mainly due to the leakage of these enzymes from the liver cytosol into the blood stream (Navarro et al., 1993), which gives an indication on the hepatotoxic effect of alloxan. On the other hand, treatment of the diabetic rats with either onion or garlic caused reduction in the activity of these enzymes in plasma (Table 2) compared to the mean values of diabetic group. These results are in agreement with those obtained by Ohaeri (2001) in rats.

The reduction in liver enzyme activities (Table 3) is mainly due to leakage of these enzymes into the blood stream as a result of alloxan toxicity which leads to the liver damage. However, treatment of alloxan diabetic groups with either onion or garlic for 28 consecutive days could restore the activities of the above enzymes to their normal levels. A possible explanation for the differential effects of onion and garlic on the activities of AST, ALT, LDH, AlP and AcP in plasma and liver is that these treatments may inhibit the liver damage induced by alloxan.

Furthermore, the improvement of the liver damage by oral administration of onion and garlic could be confirmed through studying their effect on the level of plasma bilirubin. The results in Table 1 showed that the experimentally induced diabetes increased ($p < 0.05$) the level of plasma bilirubin by 55% of control. However, onion and garlic intake produced significant ($p < 0.05$) decrease in plasma bilirubin of alloxan-diabetic rats by 28% and 25%, respectively compared to the diabetic rats. Rana et al. (1996) reported that the increase in plasma bilirubin (hyper-bilirubenimia) may be resulted from the decrease of liver uptake, conjugation or increase bilirubin production from hemolysis and this finding coincided with the decrease in total erythrocyte counts (data not shown). Also, the elevation in plasma bilirubin indicates liver damage as confirmed by the changes in the activities of plasma (Table 2) and liver (Table 3) enzymes.

Like many chronic diseases, diabetes is widely believed to increase oxidative stress. In diabetes an increase in oxidative stress arises due to compromise in natural antioxidant mechanisms and an increase in oxygen free radical production (Baynes and Thorpe, 1999). The induction in the levels of free radicals in alloxan-diabetic rats, and the decrease in these levels after treatment of alloxan-diabetic rats with onion and garlic (Tables 2–5) are in agreement with those obtained by Baynes and Thorpe (1999), Kumari and Augusti (2002), Sheweita et al. (2002), Anwar and Meki (2003)

and Campos et al. (2003). Also, Pedraza-Chaverri et al. (2000) reported that onion and garlic were effective in preventing or ameliorating oxidative stress. Maintenance of free radical levels in onion- and garlic-treated diabetic animals might be due to the presence of S-methylcysteine sulfoxide in onion (Kumari and Augusti, 2002) and S-allyl cysteine sulfoxide in garlic (Augusti and Sheela, 1996).

Glutathione S-transferases (GSTs) are a family of enzymes that catalyze the addition of the tripeptide glutathione to endogenous and xenobiotic substrates which have electrophilic functional groups. They play an important role in the detoxification and metabolism of many xenobiotic and endobiotic compounds (Ji et al., 1992). So far, few studies have been directed towards the influence diabetes millitus and hypoglycemic onion and garlic on the activity of GST (Sheweita et al., 2002; Anwar and Meki, 2003). The increment in the activity of GST (Tables 3–5) is in consistent with the induction in the generation of free radicals (Tables 2–5). Increased GST activity might be one of the defense mechanism in these animals to detoxify or neutralize the toxic metabolites, e.g. ketone bodies, generated in liver by the diabetes. Anwar and Meki (2003) suggested that garlic oil may effectively normalize the impaired antioxidants status in streptozotocin induced-diabetes. The effects of this antioxidant may be useful in delaying the complicated effects of diabetes as retinopathy, nephropathy and neuropathy due to imbalance between free radicals and antioxidant systems.

From the above results, it could be concluded that onion and garlic are able to normalize the blood glucose levels. In addition, these plant juices could ameliorate the impaired renal function, inhibit liver damage and induced free radicals associated with alloxan diabetes.

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