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Research Article
Oral Intake of Aged Garlic Extract (AGE) Ameliorates Oxidative Stress and Other Streptozotocin-induced Diabetic Complications in Rats

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Abstract

Background and Objective: Aged Garlic Extract (AGE), an aqueous extract of ethanol-soaked macerated garlic, contains many of raw garlic's bioactive components; however, causes considerably fewer physically and socially unpleasant side effects. This study aimed to investigate the antidiabetic and antioxidant potentials of oral intake of AGE (Kyolic, Wakunaga-USA) in streptozotocin (STZ, 60 mg kg^{-1}) induced diabetic rats. **Methodology:** Diabetic rats (blood sugar $\geq$20 mM) were divided into 2 groups and daily given a single oral dose of either normal saline (0.5 mL, control diabetic: C-D) or AGE (600 mg kg^{-1}, AGE-diabetic: AGE-D). Normal rats given normal saline (0.5 mL, C-N) were included for comparison and all treatments were carried out for a period of 8 weeks. Body weight, blood glucose and 24 h food and water intake were measured weekly. Serum, liver and kidney total antioxidants were determined as trolox equivalent antioxidant capacity. Serum insulin, total cholesterol and triglycerides were determined using commercial kits. Catalase was assessed using H_2O_2 as substrate. Lipid peroxidation was determined by reaction of malondialdenyde (MDA) with thiobarbituric acid. Serum fructosamine and liver protein oxidation were assessed colorimetically. A $p<0.05$ was considered significant using ANOVA and independent sample t-test. **Results:** Compared to C-N, the C-D rats showed significant weight loss and decrease in serum insulin and serum, kidney and liver total antioxidants levels and catalase activity ($p< 0.05$). Concurrently, the C-D rats had elevated food and water intake and urine output, blood glucose, serum cholesterol, triglycerides, fructosamine, MDA levels in kidney and liver and liver protein oxidation. Compared to C-D rats, the orally treated AGE-D rats demonstrated significantly increased body weight and serum insulin ($p<0.05$) as well as significantly decreased food and water intake, urine output, blood glucose and serum cholesterol, triglycerides and fructosamine ($p<0.05$). Indicators of oxidative stress were significantly ameliorated in serum, liver and kidneys of AGE-D rats ($p<0.05$). **Conclusion:** The data of this study suggested that oral intake of AGE ameliorates oxidative stress and other complications of diabetes in STZ-induced diabetic rats.

Key words: Aged garlic extract, oral intake, diabetic complications, oxidative stress

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

INTRODUCTION

Garlic (*Allium sativum* Linn) has been used for centuries as a medicinal food[1]. In the last few decades, many of the biological and medical effects of garlic have been described including anticancer[2,3], antithrombotic[4,5], cardio-protective[6-8] and antidiabetic[9,10] properties. However, raw garlic consumption as a medicinal agent is hampered by its pungent odor and potentially adverse physical effects, such as gastrointestinal distress[11,12]. Many of these negative effects of raw garlic intake have been attributed to its content of allicin and other lipid-soluble sulfur compounds[13].

For the last several years, a number of research groups have been studying the antidiabetic effects of raw garlic extract. In the streptozotocin (STZ)-induced rat model of type I Diabetes Mellitus (DM), raw garlic extract has been shown to ameliorate many of the physical symptoms of DM including weight loss, polyphagia, polydipsia and hypertension[9,14]. In addition, it has been well established that treatment with raw garlic extract leads to improvement in many of the biochemical abnormalities typical of the STZ-induced model such as hyperglycemia, hypoinsulinemia, hypercholesterolemia, hypertriglyceridemia and oxidative stress[10] as well as protecting both the liver and kidneys from the damaging effects of DM[10,15]. However and as stated above, the physically and socially un-tolerated and un-acceptable side effects of raw garlic prompted the search for a more practical and alternative garlic preparation that is more amenable to human consumption.

Aged Garlic Extract (AGE), a commercially available product (Kyolic, Wakunaga-USA) is prepared from the aqueous extract of 20 months ethanol-soaked raw macerated garlic cloves at room temperature[16]. The composition of AGE is well established and reported to contain lipid-soluble allyl sulfides, water-soluble allyl amino acids, saponins and flavonoids[17]. However, AGE contains no allicin[17]. In addition, AGE has many of the medicinal effects of raw garlic and is particularly well known for its antithrombotic and antioxidant properties[18].

Few reports are available in the literature on the effects of AGE in DM[19,20]. In a recent study, intraperitoneal (IP) administration of AGE was reported to lead to an improvement in diabetic indicators in STZ-induced diabetic rats including both physical and biochemical abnormalities[21]. However, as IP administration is clearly not a practical approach of administration in humans, the current study assessed the effects of oral administration of AGE in STZ-induced diabetic rats for a period of 8 weeks.

MATERIALS AND METHODS

Aged garlic extract: The Aged Garlic Extract (AGE-Kyolic, Wakunaga, USA) used in this study is a commercially available product as a liquid suspension (240 mg AGE mL^{-1}) and was purchased from the local market.

Animals: The animals used in this study were male Sprague-Dawley rats that had initial weights of 150-180 g and maintained on normal diet and tap water *ad libitum* for the duration of the experiment.

Induction of diabetes: The diabetic rats used in this study were produced by intraperitoneally injecting freshly prepared streptozotocin (STZ) at 60 mg kg^{-1} b.wt., into a selected number of rats as previously described by Thomson *et al.*[9]. To ascertain the induction of diabetes, whole blood glucose level was quantified in a drop of tail blood with a One Touch Ultra Easy glucometer (LifeScan UK) 5 days post-STZ injection[22].

Animals' groups and treatments: Diabetic rats (blood glucose $\geq$20 mM) were divided into two groups: Control diabetic (C-D) rats that were orally given a daily dose of normal saline and AGE-treated diabetic (AGE-D) rats that orally received a daily dose of 600 mg kg^{-1} of AGE (diluted 1:1 with distilled water). An additional group of control normal (C-N) rats were orally given normal saline (0.5 mL day^{-1}) and used for reference. All oral treatments were administered by gastric gavage. All treatments were carried out for a period of 8 weeks and each group consisted of 10-14 rats.

Collection of physical parameters: The weights of the rats in each group were recorded before the start of the experiment and then weekly during the experimental period. Twenty four hours water and food intake were also measured weekly and averaged over the 8 week experimental period. Twenty four hours urine output for each group was measured before STZ administration and at weeks 2, 4 and 8 by housing the animals in metabolic cages.

Collection of blood and serum samples: After the end of the treatment period, the rats were sacrificed after overnight fasting under sodium pentobarbitone anesthesia (10 mg kg^{-1}, May and Baker, England). Blood was collected by cardiac puncture and allowed to clot for 30 min at room temperature followed by centrifugation at 1000×g for 15 min. The separated serum was collected and stored at -40°C for later analysis. Immediately after blood collection the kidneys and livers were removed, the kidneys were decapsulated and then,

both organs were washed with normal saline, blotted with filter paper and stored at -40°C for later use.

Preparation of tissues homogenates: Homogenates of kidney and liver tissues were prepared separately as previously described by Thomson *et al.*[21]. Briefly, 1 g of each organ tissue was suspended in 3 mL of tris-HCl buffer (0.05 M, pH 7.6) and homogenized. After standing on ice for 5 min, the homogenate was centrifuged at 8000×g for 15 min at 4°C. The soluble supernatant was removed and stored in small aliquots at -40°C for further analysis.

Biochemical analysis of blood, serum and tissue components: Whole blood glucose levels were determined after overnight fasting at weeks 2, 4 and 8 of the treatment period using a glucometer. Serum total water-soluble antioxidants were determined by the method of Miller *et al.*[23] as modified by Drobiova *et al.*[24]. Serum insulin was determined by ELISA using kits supplied by SPIbio (France). Serum total cholesterol and triglycerides were determined colorimetrically using kits supplied by Randox (USA). Serum fructosamine was quantitated by reaction with nitrobluetetrazolium as described by Chung *et al.*[25]. Serum and tissue catalase activity was determined as described by Aebi[26]. Lipid peroxidation was assessed by reaction of malondialdehyde with thiobarbituric acid by the method of Ohkawa *et al.*[27]. Oxidative protein damage was assessed colorimetrically by reaction with 2,4-dinitrophenylhydrazine (DNPH)[28] using a kit supplied by Cayman Chemical Company (USA). Total serum and tissue protein levels were determined using the coomassie blue dye binding method of Bradford[29].

Statistical analysis: Data are expressed as Mean±SEM. Data within a group were compared using one way ANOVA and data among groups were compared using the independent sample t-test (SPSS v.17.1). A $p<0.05$ was considered significant[30].

Guidelines for animal's care and use: All experimental procedures were approved by the Animal Care and Use Committee, Faculty of Science, Kuwait University and also complied with the guidelines in the Guide for the Care and Use of Laboratory Animals of the National Research Council (USA)[31].

RESULTS

Physical parameters: During the experiment, the three groups of rats demonstrated different body weight changes that culminated at the last week. First, the C-N rats steadily gained body weight which more than doubled at week 8. Conversely, the C-D rats steadily lost weight reaching a low of 45% of their initial body weight at week 8. In comparison, AGE-D rats recovered in terms of body weight after an initial loss post-STZ in the first week, then showing a significant increase ($p<0.05$) in weight reaching a high of 20% above their initial weight at the last week. Compared to the C-D rats, the AGE-D rat's body weight was more than 121% higher at the end of the study (Fig. 1).

The C-D rats greatly increased food and water intake during the experiment by 68 and 400%, respectively compared to C-N rats (Table 1). Alternatively, AGE-D rats' food and water intakes were both significantly less by 26%, compared to C-D rats. In comparison, the C-D rat's urine

Table 1: Oral AGE decreased urine output and food and water intake of diabetic rats

Groups	*Food intake (g/24 h)	*Water intake (mL/24 h)	#Urine output (mL/24 h)
C-N	25±2	50±2	8±0.7
C-D	42±1[a]	250±5[a]	95±0.6[a]
AGE-D	31±1[a,b]	185±3[a,b]	83±0.6[a,b]

C-N: Normal control, C-D: Diabetic control, AGE-D: AGE-treated diabetic.*Food and water intake are averaged over the 8 week experimental period. #Urine output values measured at week 8. Data are Mean±SEM, a: $p<0.05$ vs C-N, b: $p<0.05$ vs C-D

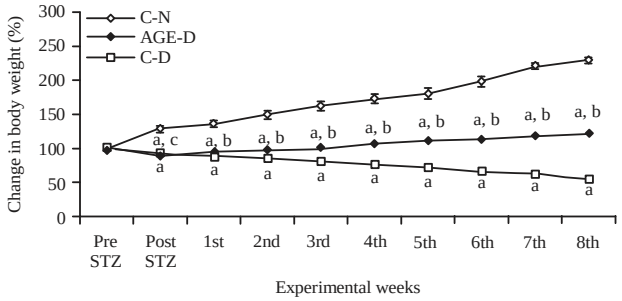

Fig. 1: Effect of oral AGE on body weight of diabetic rats

Each rat was weighed before STZ injection (Pre STZ), 1 week after STZ injection (Post STZ) and weekly for the 8 weeks of the experiment. Data are Mean±SEM, a: $p<0.05$ vs C-N, b: $p<0.05$ vs C-D, c: No significant difference vs C-D

output was over 10 times higher than that of C-N rats. At the same time, treated AGE-D rat's urine output was significantly reduced by 13% compared to C-D rats.

Biochemical parameters: The whole blood glucose level of all rats groups were assessed before treatment and 5 days post STZ, at week 4 and at the end of the treatment period at week 8 (Fig. 2). The blood glucose levels post-STZ in C-D rats were higher by nearly 2-fold compared to C-N rats. The C-D rats higher blood glucose levels continued to increase throughout the experimental period reaching 200% at week 4 and 243% at week 8. In comparison, although the AGE-D rats showed an equivalent increase in blood glucose before treatment (post-STZ), however at 4 and 8 weeks of AGE treatment, these animals had significantly lower ($p<0.05$) blood glucose levels at 22 and 47% , respectively, compared to the C-D group. Although AGE-D rats had a lower blood glucose concentration, their blood glucose values were still significantly higher by 135 and 82%, respectively, at weeks 4 and 8 compared to the C-N rats.

Induction of diabetes with STZ resulted in over 10-fold reduction in serum insulin levels in the C-D rats at the end of the experiment compared to the C-N rats. In comparison and at the same time, the AGE-D rats exhibited over 5 fold higher serum insulin concentration compared to the C-D rats. In contrast and in agreement with blood glucose levels, serum fructos amine levels were significantly increased by 161% after 8 weeks in C-D rats compared to the C-N group. Oral treatment with AGE significantly decreased serum fructosamine by approximately 34% in AGE-D rats compared to the C-D group (Fig. 3).

Serum cholesterol was significantly increased by 63% in C-D rats compared to C-N rats. Treatment with AGE significantly lowered serum cholesterol by 32% in AGE-D rats (Fig. 4). Similarly, serum triglycerides were significantly increased by 169% in C-D rats compared to the C-N group. The AGE-D rats exhibited significantly lower serum triglycerides reaching 36% less than the C-D group. Although significantly lower compared to the C-D rats, both serum cholesterol and triglycerides were significantly higher in the AGE-D rats (12 and 73%, respectively) compared to the C-N rats (Fig. 4).

Antioxidant parameters: Serum total antioxidant levels and catalase activity were significantly decreased by 26 and 71%, respectively, in C-D rats compared to C-N rats. The AGE treatment resulted in significantly increased serum antioxidants by 23% and serum catalase by 100%

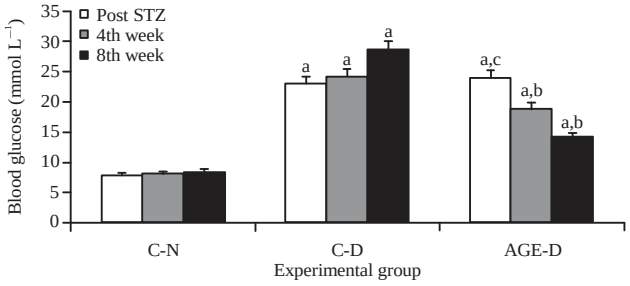

Fig. 2: Effect of oral AGE on blood glucose level of diabetic rats

Blood glucose levels (mmol L^{-1}) were measured 1 week after STZ injection (Post STZ) and at weeks 4 and 8 of the experiment. Data are Mean±SEM, a: $p<0.05$ vs C-N, b: $p<0.05$ vs C-D, c: No significant difference vs C-D

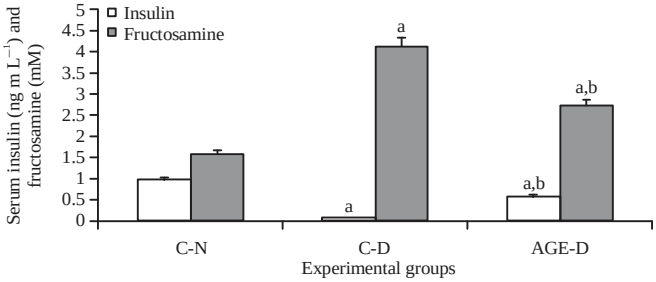

Fig. 3: Effect of oral AGE on serum insulin and fructosamine levels of diabetic rats

Serum insulin (ng mL^{-1}) and fructosamine (mM) levels were measured at the conclusion of the treatment period (8 weeks). Data are Mean±SEM, a: $p<0.05$ vs C-N and b: $p<0.05$ vs C-D

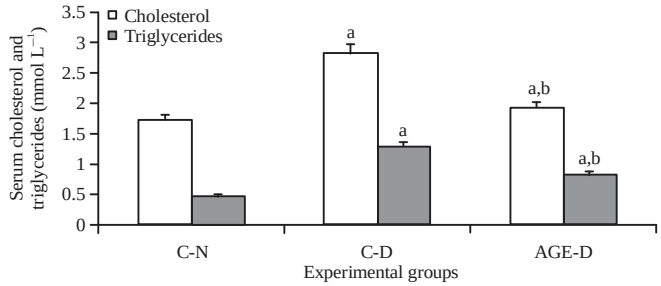

Fig. 4: Effect of oral AGE on serum triglyceride and cholesterol levels of diabetic rats

Serum triglyceride and cholesterol levels (mmol L^{-1}) were measured at the conclusion of the treatment period (8 weeks). Data are Mean±SEM, a: p<0.05 vs C-N and b: p<0.05 vs C-D

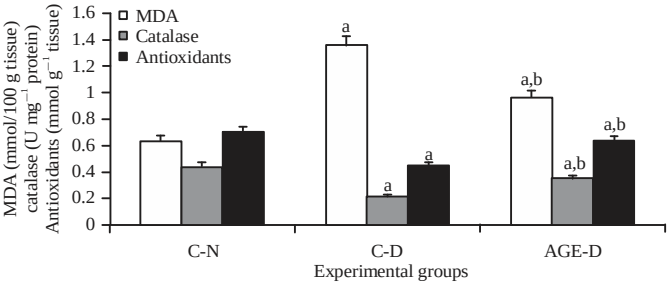

Fig. 5: Effect of oral AGE on kidney malondialdehyde (MDA) and antioxidant levels and catalase activity of diabetic rats

MDA levels (mmol/100 g tissue), total antioxidants (mmol g^{-1} tissue) and catalase activity (U mg^{-1} protein) were determined in kidney tissue at the conclusion of the treatment period (8 weeks). Data are Mean±SEM, a: p<0.05 vs C-N and b: p<0.05 vs C-D

compared to the C-D rats. Although significantly increased (p<0.05), the serum antioxidant levels and catalase activity in the AGE-D rats were still significantly less that the C-N rats by 9 and 43%, respectively (Table 2).

As indicators of antioxidant status, total antioxidant levels, catalase activity and MDA levels were assessed in both kidney and liver tissues of the 3 groups of rats. In kidney tissues (Fig. 5), both total antioxidant levels and catalase activity were decreased by 36 and 51%, respectively, in C-D rats compared to C-N animals. In comparison, the AGE-D rats exhibited significantly increased kidney total antioxidant levels of 41% and catalase activity of 63% compared to C-D rats. In contrast, MDA levels, an indicator of lipid peroxidation, were more than doubled in kidneys of C-D rats compared to C-N rats. In kidneys of AGE-D rats, MDA levels were significantly decreased by 29% compared to C-D rats. Although all these three indicators of antioxidant status were significantly ameliorated in kidneys by AGE treatment, the values were still significantly different (p<0.05) from C-N rats at the end of week 8 of the experiment.

Similarly, in liver tissues (Fig. 6), total antioxidant levels and catalase activity were decreased by 39 and 52%, respectively, in C-D rats compared to C-N animals. Treatment with AGE resulted in significantly higher liver total antioxidant levels of 49% and catalase activity of 23% compared to C-D rats. As in kidney tissues, liver MDA levels were significantly higher in C-D rats by 44% compared to C-N rats. In livers of AGE-D rats, MDA levels were significantly decreased by 23% compared to C-D rats. Similar to the results described for both serum and kidney, although these three indicators of antioxidant status were significantly ameliorated in livers by AGE treatment, the values were still significantly different (p<0.05) from C-N rats at the end of the 8 week experiment.

Table 2: Oral AGE increased serum antioxidant levels and catalase activity in diabetic rats

Groups	Antioxidants levels (mM)	Catalase activity (U mg^{-1} protein)
C-N	17.4±0.07	2.1±0.050
C-D	12.9±0.04^{a}	0.6±0.002^{a}
AGE-D	15.9±0.02^{a,b}	1.2±0.040^{a,b}

C-N: Normal control, C-D: Diabetic control, AGE-D: AGE-treated diabetic, data are Mean±SEM, a: p<0.05 vs C-N, b: p<0.05 vs C-D

Liver protein levels were significantly decreased by 11% in C-D rats compared to C-N rats, while oral AGE administration significantly increased liver protein by 7% in

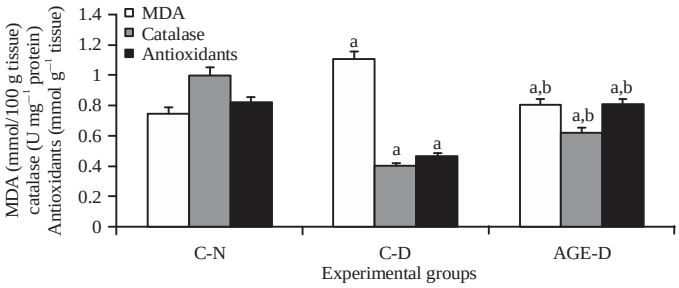

Fig. 6: Effect of oral AGE on liver malondialdehyde (MDA) and antioxidant levels and catalase activity of diabetic rats
MDA levels (mmol/100 g tissue), total antioxidants (mmol g^{-1} tissue) and catalase activity (U mg^{-1} protein) were determined in liver tissue at the conclusion of the treatment period (8 weeks). Data are Mean±SEM, a: $p < 0.05$ vs C-N and b: $p<0.05$ vs C-D

Table 3: Oral AGE increased total liver protein and decreased carbonyl protein in diabetic rats

Group	Total protein (mg g^{-1} tissue)	Carbonyl protein (nmol mg^{-1} protein)
C-N	47.95±1.23	3.48±0.985
C-D	43.01±1.34[a]	7.38±1.003[a]
AGE-D	46.08±0.85[a,b]	4.54±0.9328[b,d]

C-N: Normal control, C-D: Diabetic control, AGE-D: AGE-treated diabetic, data are Mean±SEM, a: $p<0.05$ vsC-N, b: $p<0.05$ vs C-D, d: No significant difference vs. C-N

AGE-D rats (Table 3). In comparison, carbonyl protein, a measure of protein oxidation, was significantly increased by over 2 fold in C-D rats compared to C-N rats with AGE treated diabetic rats exhibiting liver carbonyl protein levels significantly lower by 39% than C-D rats and not significantly different compared to C-N rats.

DISCUSSION

The use of natural medicines in the treatment of chronic illness has become common in the last two decades. The World Health Organization (WHO) estimates that 80% of the world population uses complementary and alternative medicines (CAMs) in their primary health care[32]. In the United States, the use of CAMs by chronic disease sufferers has become widespread reaching as high as 53%[33]. In the Arab regions, recent reports have suggested that CAMs use is also common[34-36].

The use of CAMs and in particular dietary supplements is also a common practice by diabetic patients. In the United States, it has been reported that about 57% of diabetic patients use CAMs[37]. The prevalence of CAMs use in diabetic patients is higher in countries that commonly use natural medicines. For example in Mexico, 62% of type 2 diabetic patients reported the use of CAM therapies[38]. Two recent studies have quantitated CAMs use in diabetic patients in Malaysia in the range of 50-62%[39,40]. Ching *et al.*[39] reported that 13.3% of diabetic patients consumed garlic as a CAM.

In the last few decades, many reports have indicated that various garlic preparations have beneficial medicinal effects including in DM. We have reported similar effects of raw garlic extract in the STZ-induced rat DM model[9,10]. However, since the use of raw garlic is accompanied with unpleasant effects, such as strong odor and occasionally gastrointestinal distress, investigation of the anti-diabetic potential of AGE, a well-known commercial product, in the STZ-induced rat model of DM was undertaken.

In the current study, the effects of oral administration of AGE at a dose of 600 mg kg^{-1} in STZ-induced diabetic rats were investigated. This study complements a previous dose-response investigation of intraperitoneal (IP) AGE administration effect in the same rat model in which a dose of 600 mg kg^{-1} was determined to be most effective in ameliorating diabetic indicators[21]. The findings of this study confirmed that oral AGE administration is effective in attenuating both physical and biochemical indices of DM in this model of type I diabetes.

Oral intake of AGE ameliorates physical symptoms of DM: As expected, administration of STZ and subsequent development of hyperglycemia led to a progressive loss of body weight in the C-D rats so that, at the end of the experiment, these rats were about 42% lighter than at the start of the study, while the C-N rats were more than double their initial weight. This observation is in agreement with many studies on the progression of DM in STZ-induced rats[21,41,42]. Oral AGE treated diabetic rats recovered significantly in terms of weight loss and subsequently increased their weights about 21% compared to their initial weight. These results are comparable to previous observations in STZ-induced diabetic rats treated with the same IP dose of AGE[21].

Prolonged hyperglycemia as seen in STZ-induced DM rat model and confirmed in the present study (Fig. 2) leads not only to weight loss but also polyphagia, polydipsia and

polyuria as seen in untreated type I DM in humans. In the current study, the C-D rats experienced very marked increases in food (68%) and water (400%) intake as well as urine output (>10-fold higher) that were partially but significantly reduced ($p<0.05$) by oral AGE treatment. These results are nearly equivalent to the changes observed with the same dose of AGE (600 mg kg^{-1}) that was administered IP and reported previously by Thomson *et al.*[21]. In addition, Shiju *et al.*[20] observed a similar effect of a 500 mg kg^{-1} oral AGE dose in lessening polyuria in the STZ-induced rat model of type I DM.

In general, oral AGE-treated diabetic rats were healthier and did not exhibit the severe effects of DM seen in the untreated C-D rats. These observations are in agreement with previous studies involving IP administration of both raw garlic extract and AGE[10,21].

Oral AGE ameliorates biochemical indicators of DM: As reported here, prolonged hyperglycemia and hypoinsulinemia in the C-D rats lead to elevation of serum fructosamine, an indicator of glycemic control[43,44]. Oral AGE treatment of the diabetic rats resulted in a marked decrease in blood glucose so that at the end of the experiment (week 8), the AGE-D rats had blood glucose levels that were 47% less than the C-D rats. This hypoglycemic effect of AGE coincided with an increase in serum insulin levels and improved glycemic control as reflected by decreased serum fructosamine levels in the AGE-D rats. These changes indicate that the oral AGE is reversing hyperglycemia and hypoinsulinemia typical of the STZ-induced model of type I DM. In addition, these changes are in agreement to those observed previously in diabetic rats treated with IP AGE[21], suggesting that the oral route of administration is also effective in treatment of diabetic rats.

The increase in serum insulin levels in the AGE-D rats suggests that the administration of AGE allows restoration of pancreatic β-cells ability to synthesize and secrete insulin. This observation is in agreement with the study of Moradabadi *et al.*[45] who showed increased expression of insulin mRNA in the pancreas of raw garlic-treated alloxan-induced diabetic rats. Thus, investigation of this aspect of the effects of AGE requires further study.

Recently, Asdaq[18] reported that AGE administration to female Sprague-Dawley rats fed either normal or high fat diet led to lowering of serum triglycerides and total cholesterol. Similarly in the present study, the C-D rats had increased serum triglyceride and cholesterol levels that were reduced by 73 and 12%, respectively with oral AGE treatment. Again, this result is in agreement with a previous study in IP AGE-treated diabetic rats[21] as well as the report of Shiju *et al.*[20].

Oral AGE improves oxidative stress in diabetic rats: Numerous studies have established a link between increased Oxidative Stress (OS), hyperglycemia and diabetic complications in both humans and animal models[46-48]. It has been well established by this group and others that raw garlic extract is effective in ameliorating OS in the STZ-induced rat model of DM[10,49]. In addition, the antioxidant potency of AGE has been studied extensively and has been shown to ameliorate OS in several conditions including DM[21], thrombosis[50] and liver and renal injury[51,52].

A previous study established that AGE ameliorates OS in STZ-induced diabetic rats when administered IP[21]. In agreement with this report, in the current study oral AGE administration markedly improved the antioxidant status in serum, liver and kidney of diabetic rats as reflected by increased total antioxidants and catalase activity as well as decreased lipid peroxidation (MDA) in kidney and liver tissues. Additionally, the improved antioxidant status is reflected by a decreased liver protein oxidation, an alternative measure of OS[53,54]. In agreement, Balamash and coworkers reported decreased serum lipid hydroperoxides in type 2 DM patients treated with AGE (3000 mg day^{-1}) for 3 months[19].

It has been suggested that the abundant compound in AGE, S-allylcysteine (SAC), is a major contributor to the anti-diabetic and antioxidant activity of AGE[18,21,55,56]. Saravanan and Ponmurugan[56] reported that SAC treatment of STZ-induced diabetic rats (at doses of 100 and 150 mg kg^{-1}) had significant anti-diabetic effects suggesting the SAC may be the major contributor to diabetes-alleviating effects of AGE. In addition, SAC has been shown to have significant antioxidant potential both in diabetic models[57,58] as well as other conditions of OS[59-62]. Colin-Gonzalez *et al.*[55] have suggested that both AGE and SAC induce antioxidant enzymes as we have observed in this study. Thus, at least part of the antioxidant effect of AGE appears to be due to this antioxidant enzyme inducing property.

CONCLUSION AND FUTURE RECOMMENDATIONS

The observed beneficial effects of oral intake of AGE in the STZ-induced rat model of DM suggest that this easily obtainable, stable preparation may be useful as an adjuvant therapy in DM. The study is limited as the effects of AGE were assessed only in a type I model of DM while type 2 DM is more prevalent. Therefore further investigations should evaluate the effects of AGE in type 2 DM as well as carrying out studies on diabetic patients to determine the usefulness of AGE in human subjects.

SIGNIFICANCE STATEMENTS

- Oral AGE treatment elicits improvement of physical abnormalities that develop in diabetes
- Oral AGE helps to reverse the hyperglycemia and lipid abnormalities that occur in diabetes
- Oral AGE treatment results in improvement of oxidative stress that is prevalent in diabetes

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