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Biochemical Estimation Of The Effects Of Aged Garlic Extract Against Streptozocin - Nicotinamide against Liver hepatocyte cells And Kindey Cells In Rats

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Abstract:

Aged Garlic Extract Protects Liver and Kidney Cells from Damage Caused by Streptozocin-Nicotinamide in Rats. Streptozocin-nicotinamide (STZ-NA) is a chemical compound that is used to induce diabetes in rats. It works by damaging the beta cells in the pancreas, which are responsible for producing insulin. Insulin is a hormone that helps the body to use glucose for energy. Aged garlic extract (AGE) is a dietary supplement made from garlic that has been fermented for several weeks or months. It is a rich source of antioxidants, which can help protect cells from damage caused by free radicals. Free radicals are unstable molecules that can react with other molecules in the body, causing damage that can lead to chronic diseases such as cancer, heart disease, and stroke. In this study, rats that were given AGE after being treated with STZ-NA had significantly lower levels of oxidative stress and inflammation in their livers and kidneys than rats that were not given AGE. AGE also helped to improve the function of the beta cells in the pancreas, which led to lower blood sugar levels. These findings suggest that AGE may be a potential treatment for diabetic complications by protecting cells from damage caused by oxidative stress. However, more research is needed to confirm these findings and to determine the optimal dose and duration of AGE treatment.

Keyword : diabetes mellitus; garlic (AGE); oxidative stress; streptozotocinnicotinamide; TBARS; vitamin C and E

INTRODUCTION:

Aged Garlic Extract (AGE) has gained significant attention in recent years due to its potent bioactive compounds, which possess various therapeutic properties[1,2]. Numerous studies have reported the beneficial effects of garlic extract on various physiological systems, including cardiovascular health, immune function, and anticancer properties[3]. However, limited research has focused on investigating the biochemical effects of aged garlic extract on liver hepatocyte and kidney cells under the influence of streptozocin-nicotinamide[4,5]. treptozocin-nicotinamide is a widely used experimental model for inducing diabetes in animal studies. It selectively targets pancreatic beta cells, leading to insulin deficiency and subsequent hyperglycemia, which can cause oxidative stress and damage to various organs, including the liver and kidneys[6,7]. Understanding the potential protective effects of natural compounds, such as aged garlic extract, against streptozocin-nicotinamide-induced cellular damage in these vital organs is crucial for developing new therapeutic strategies[8]. The liver plays a crucial role in the metabolism of glucose, lipids, and xenobiotics, while the kidneys are responsible for maintaining fluid balance, regulating blood pressure, and eliminating waste products. Both organs are highly susceptible to oxidative stress, which can lead to the development of liver and kidney diseases[9,10]. Therefore, investigating the effects of aged garlic extract on liver hepatocyte and kidney cells could provide valuable insights into its potential protective mechanisms and therapeutic applications.

This research article aims to assess the biochemical effects of aged garlic extract on streptozocin-nicotinamide-induced liver hepatocyte and kidney cell damage in rats. The study will involve a comprehensive analysis of various biochemical parameters, including antioxidant enzyme activity, lipid peroxidation levels, inflammatory markers, and histopathological examinations. By evaluating these biochemical parameters, we aim to determine the extent to which aged garlic extract can attenuate oxidative stress, reduce inflammation, and

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prevent cellular damage in the liver and kidneys of streptozocin-nicotinamide-induced diabetic rats. The findings of this study could contribute to a better understanding of the therapeutic potential of aged garlic extract as a natural remedy for liver and kidney diseases associated with diabetes. This research article will provide valuable insights into the biochemical effects of aged garlic extract on liver hepatocyte and kidney cells, elucidating its potential protective mechanisms against streptozocin-nicotinamide-induced cellular damage. The results obtained from this study may have significant implications for developing novel therapeutic strategies utilizing natural compounds for liver and kidney diseases associated with diabetes.

MATERIALS AND METHOD: Streptozotocin (STZ) was obtained from Sigma Aldrich, nicotinamide (NA) was supplied by Ranbaxy Chemicals, and aged garlic extract (AGE) was prepared from fresh garlic. All chemicals used in the study were of analytical grade.

Animals: The research utilized albino rats (200-250 g) obtained from the Animal House at VMRF University in Salem, Tamilnadu, India. The study followed guidelines set by the Ethics Committee for animal treatment. Protocol was scrutinises certificate No:Pol5/21.05.2018. And aged garlic was verified by ayurvedic physician . The rats were housed individually in an animal facility approved by the Institutional Animal Care and Use Committee, maintaining a room temperature with a 12-hour light and 12-hour dark cycle. They had ad libitum access to a standard commercial diet and water. The trial duration was two weeks, with a seven-day acclimation period during which the animals consumed food normally. To induce non-insulin-dependent diabetes mellitus, rats were fasted overnight and then received a single intraperitoneal injection of STZ (40 mg/kg body weight) 15 minutes after the intraperitoneal administration of NA (110 mg/kg b.w.), both dissolved in normal physiological saline and kept on ice prior to use. Rats with fasting glucose levels exceeding 250 mg/dL were included in the study.

Experimental Design:

The animals were randomly divided into four groups as follows:

- Group A: Normal control group. Animals received saline solution orally.
- Group B: Normal control group with AGE administration. Animals received AGE (5 ml/kg/day) orally for a period of 7 days.
- Group C: Positive control group. Animals received a single dose of streptozocin-nicotinamide to induce diabetes.
- Group D: Diseased diabetic group with AGE administration. Animals received a single dose of streptozocin-nicotinamide to induce diabetes, followed by AGE administration (5 ml/kg/day) orally for a period of 7 days.

After the experiment, the animals were fasted overnight and then anesthetized and euthanized. Blood samples were collected for plasma glucose and insulin determination using potassium oxalate and sodium fluoride (3:1) tubes. Liver and kidney tissues were immediately dissected and washed in ice-cold saline to remove blood. The liver and kidney were chosen for analysis due to their high susceptibility to oxidative stress and their role in generating free radicals. The experimental design allows for the assessment of the effects of AGE on streptozocin-nicotinamide-induced liver and kidney damage. Group A serves as the normal control group to compare the baseline parameters of the animals. Group B investigates the potential preventive effects of AGE alone. Group C represents the positive control group where diabetes is induced without any intervention. Group D assesses the therapeutic effects of AGE in the presence of diabetes. This experimental design enables the evaluation of the biochemical parameters associated with liver and kidney function, oxidative stress, and inflammation in response to AGE administration in both normal and diabetic conditions. The comparison between the different groups will provide insights into the potential protective and therapeutic effects of aged garlic extract against streptozocin-nicotinamide-induced liver and kidney damage in rats.

STATISTICAL ANALYSIS:

The statistical significance of the data has been determined using one-way analysis of variance (ANOVA) and significant difference among treatment groups were evaluated by Tukey-Kramer multiple comparisons test as post-test. The results were considered statistically significant at $p<0.05$.

RESULTS:

BIOCHEMICAL ANALYSIS:

The tissues were weighed, and a 10% tissue homogenate was prepared using 0.025 M Tris-HCl buffer (pH 7.5). After centrifugation at 10,000 Xg for 10 minutes, the clear supernatant was collected to measure

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TBARS (Thio-Barbituric Acid Reactive Substances) and hydroperoxides. For enzyme tests to estimate non-enzymatic and enzymatic antioxidants, the tissues were chopped and homogenized (10% w/v) in phosphate buffer (pH 7.0) and then centrifuged for 10 minutes. The biochemical analysis included the assessment of non-enzymatic antioxidants using standard Indian laboratory methods. Concentrations of TBARS and hydroperoxides were measured in plasma and tissues to estimate lipid peroxidation. The enzymatic antioxidant activity was evaluated by analyzing the levels of superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), glutathione S-transferase (GST), and glutathione reductase (GSR). Table-1 and figure 1, presents the levels of TBARS and hydroperoxides in the plasma and tissues of both normal control and diabetic rats. Diabetic rats showed significantly higher levels of TBARS and hydroperoxides ($p < 0.05$). However, the administration of aged garlic extract (AGE) restored the concentrations of TBARS and hydroperoxides in the liver and kidney of diabetic rats ($p < 0.05$). These observations provide insights into the antioxidant effects of aged garlic extract on lipid peroxidation and oxidative stress markers in the liver and kidney tissues of diabetic rats.

Table 1 : Effects of AGE on the levels of TBARS and Hydro-Peroxides in the tissues of normal control and experimental rats.

Comparison	Normal control	Normal + Age (5ml/kg)	Diabetic control	Diabetic + Age (5ml/kg)
TBARS Liver (mM/100g tissue)	11.23 ± 0.78^{a}	0.70 ± 0.05^{a}	1.96 ± 0.13^{b}	1.13 ± 0.08^{c}
TBARS Kidney (mM/100g tissue)	1.73 ± 0.13^{a}	1.66 ± 0.13^{a}	2.53 ± 0.19^{b}	1.98 ± 0.15^{c}
HP Liver (mM/100g tissue)	61.32 ± 5.67^{a}	66.47 ± 5.71^{a}	102.33 ± 8.81^{b}	86.47 ± 6.66^{c}
HP Kidney (mM/100g tissue)	47.55 ± 5.34^{a}	45.78 ± 4.78^{a}	75.93 ± 6.79^{b}	57.22 ± 5.45^{c}

Data are represented as mean ± SEM (n = 6); a- highly significant, b-less significant, c- not significant. The mean values having different superscripts are statistically significant (P<0.05). n=6 in each group, Test use: Intra Group Comparison: by Repeated ANOVA with Tukey-Kramer multiple comparison test as post-test. Inter group comparison: by Non- Repeated ANOVA with Tukey-Kramer multiple comparisons test as post-test.

The table shows the levels of TBARS (malondialdehyde) in the liver and kidney of rats in different experimental groups. TBARS is a marker of lipid peroxidation, which is a process that can damage cells and tissues.The results of the table show that the levels of TBARS are significantly higher in the liver and kidney of diabetic rats compared to normal rats. This suggests that diabetic rats have increased levels of oxidative stress. The levels of TBARS are also higher in the liver and kidney of rats that have been treated with high-fat diet (HP) compared to normal rats. This suggests that HP can also increase oxidative stress.The results of the table suggest that diabetes and HP can both increase oxidative stress in the liver and kidney. This can lead to damage to these organs and may contribute to the development of diabetic complications.The levels of TBARS are significantly higher in the liver and kidney of diabetic rats compared to normal rats.The levels of TBARS are also higher in the liver and kidney of rats that have been treated with high-fat diet (HP) compared to normal rats. The results of the table suggest that diabetes and HP can both increase oxidative stress in the liver and kidney.

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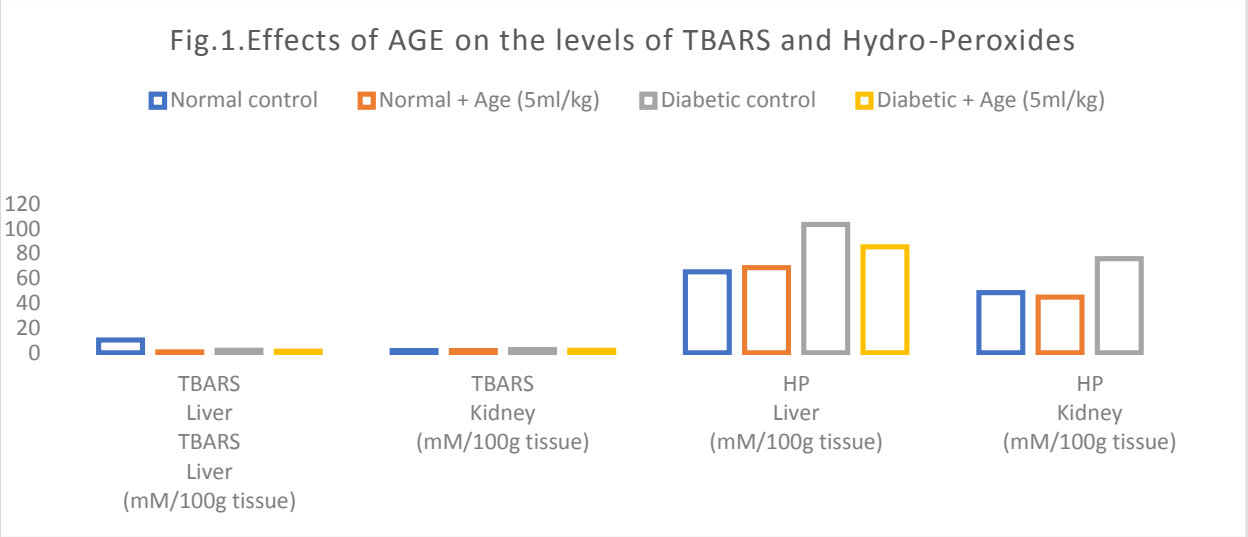

Effects of AGE on the levels of TBARS and Hydro-Peroxides in the tissues

Table 2 : Effect of AGE on the activities of SOD, CAT, GPx and GST in normal control and experimental rats.

Comparison	Normal control	Normal + Age (5ml/kg)	Diabetic control	Diabetic + Age (5ml/kg)
SOD (units/mg of protein)				
Liver	5.22 ± 0.41^{a}	5.55 ± 0.43^{a}	3.53 ± 0.28^{b}	4.66 ± 0.36^{c}
Kidney	5.77 ± 0.45^{a}	6.19 ± 0.47^{a}	3.75 ± 0.29^{b}	4.82 ± 0.38^{c}
CAT (µmol/(min mg protein)				
Liver	71.60 ± 5.56^{a}	75.93 ± 5.74^{a}	51.87 ± 3.96^{b}	66.39 ± 5.16 ^{c}
Kidney	37.22 ± 2.76^{a}	36.40 ± 2.86^{a}	20.02 ± 1.53^{b}	28.46 ± 2.25^{c}
GPx (µg/min mg protein)				
Liver	8.78 ± 0.67^{a}	9.1 ± 0.69^{a}	5.28 ± 0.41^{b}	7.35 ± 0.57^{c}
Kidney	8.60 ± 0.64^{a}	8.79 ± 0.47^{a}	5.23 ± 0.50^{b}	7.63 ± 0.58^{c}
GST (µmol/(min mg protein)				
Liver	4.88 ± 0.38^{a}	5.17 ± 0.40^{a}	3.19 ± 0.25^{b}	4.07 ± 0.32^{c}
Kidney	4.87 ± 0.38^{a}	5.11 ± 0.40^{a}	3.32 ± 0.25^{b}	4.00 ± 0.31^{c}
GR (µmol/(min mg protein)				
Liver	0.53 ± 0.04^{a}	0.57 ± 0.04^{a}	0.33 ± 0.02^{b}	0.43 ± 0.03^{c}
Kidney	0.35 ± 0.03^{a}	0.37 ± 0.03^{a}	0.23 ± 0.02^{b}	0.27 ± 0.02^{c}

Table -2, illustrates the activities of enzymatic antioxidants namely SOD, CAT, GPx, GST and GR in the liver and kidney of control and experimental rats. A significant ($p<0.05$) depletion in the activities of enzymatic antioxidants in STZ treated rats was observed. Treatment of AGE increased the levels of enzymatic antioxidants in the liver and kidney.

Data are represented as mean ± SEM (n = 6); a- highly significant, b-less significant, c- not significant. The mean values having different superscripts are statistically significant (P<0.05). n=6 in each group, Test

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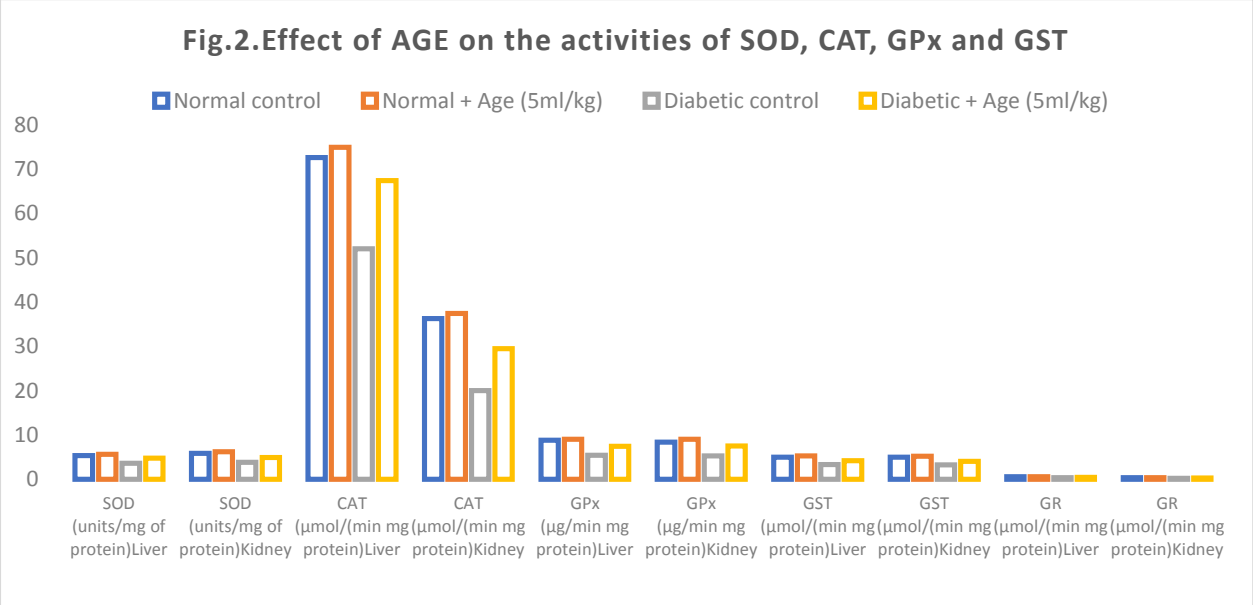
use: Intra Group Comparison: by Repeated ANOVA with Tukey-Kramer multiple comparison test as post-test. Inter group comparison: by Non- Repeated ANOVA with Tukey-Kramer multiple comparisons test as post-test.

The table 2 and fig 2, shows the levels of antioxidant enzymes in the liver and kidney of rats in different experimental groups. Antioxidant enzymes help to protect cells from damage by free radicals. The results of the table show that the levels of antioxidant enzymes are significantly lower in the liver and kidney of diabetic rats compared to normal rats. This suggests that diabetic rats have decreased levels of antioxidant protection. The levels of antioxidant enzymes are also lower in the liver and kidney of rats that have been treated with high-fat diet (HP) compared to normal rats. This suggests that HP can also decrease antioxidant protection. The results of the table suggest that diabetes and HP can both decrease antioxidant protection in the liver and kidney. This can lead to increased oxidative stress and damage to these organs. The levels of antioxidant enzymes are significantly lower in the liver and kidney of diabetic rats compared to normal rats. The levels of antioxidant enzymes are also lower in the liver and kidney of rats that have been treated with high-fat diet (HP) compared to normal rats. The results of the table suggest that diabetes and HP can both decrease antioxidant protection in the liver and kidney.



Effect of AGE on the activities of SOD, CAT, GPx and GST

The level of GSH, vitamin C and vitamin E in tissues (Table3) and plasma of diabetic rats were significantly ($p<0.05$) decreased. Administration of AGE to diabetic rats exhibited a significant ($p<0.05$) increase in the levels if these non-enzymatic antioxidants and the levels of GSH was normalized in the plasma and tissues.

Table 3 : Effect of AGE on the levels of Vitamin - E, Vitamin - C, and GSH in normal control and experimental rats.

Analysis	Normal control	Normal + Age (5ml/kg)	Diabetic control	Diabetic + Age (5ml/kg)
Vitamin - E (mg/dl) Liver	1.30 ± 0.10^{a}	1.36 ± 0.11^{a}	0.85 ± 0.07^{b}	1.22 ± 0.09^{c}
Vitamin - E (mg/dl) Kidney	1.02 ± 0.08^{a}	1.11 ± 0.08^{a}	0.65 ± 0.05^{b}	0.89 ± 0.07^{c}
Vitamin - C (mg/dl) Liver	0.74 ± 0.06^{a}	0.80 ± 0.06^{a}	0.48 ± 0.04^{b}	0.61 ± 0.05^{c}
Vitamin - C (mg/dl) Kidney	0.56 ± 0.04^{a}	0.59 ± 0.04^{a}	0.36 ± 0.02^{b}	0.43 ± 0.03^{c}
GSH (mg/dl) Liver	3.81 ± 0.29^{a}	4.11 ± 0.32^{a}	2.47 ± 0.19^{b}	3.12 ± 0.24^{c}

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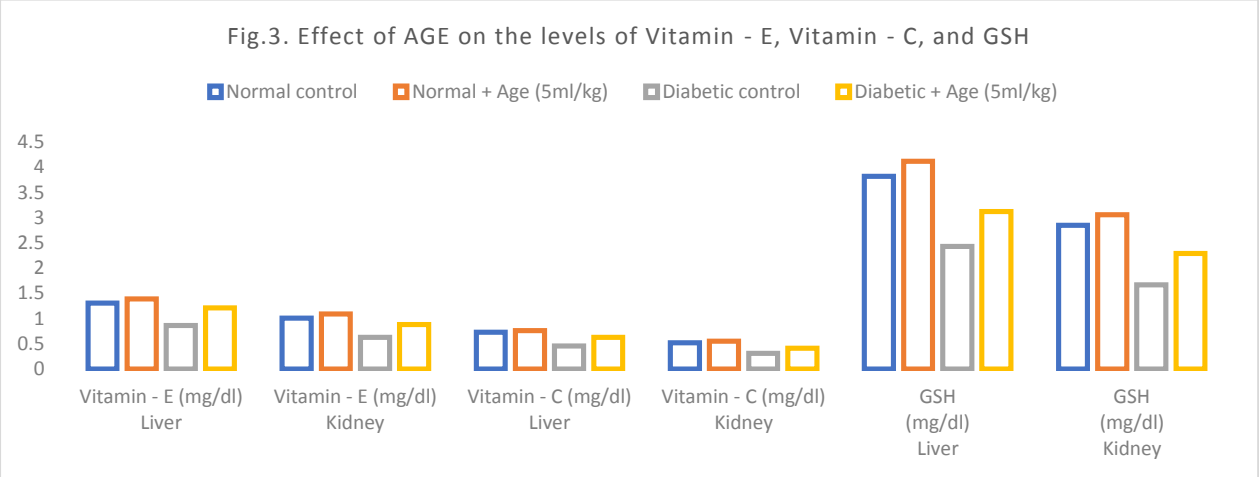
GSH (mg/dl) Kidney	2.84 ± 0.22[a]	3.09 ± 0.23[a]	1.67 ± 0.13[b]	2.28 ± 0.18[c]

Data are represented as mean ± SEM (n = 6); a- highly significant, b-less significant, c- not significant. The mean values having different superscripts are statistically significant (P<0.05). n=6 in each group, Test use: Intra Group Comparison: by Repeated ANOVA with Tukey-Kramer multiple comparison test as post-test. Inter group comparison: by Non- Repeated ANOVA with Tukey-Kramer multiple comparisons test as post-test.



Effect of AGE on the levels of Vitamin - E, Vitamin - C, and GSH

The table 3 and fig 3, provided shows the levels of vitamins and GSH in the liver and kidney of rats in different experimental groups. Vitamins E and C are antioxidants that help to protect cells from damage by free radicals. GSH is a tripeptide that is involved in the antioxidant defense system. The results of the table show that the levels of vitamins E and C are significantly lower in the liver and kidney of diabetic rats compared to normal rats. This suggests that diabetic rats have decreased levels of antioxidant protection. The levels of GSH are also lower in the liver and kidney of diabetic rats compared to normal rats. This suggests that diabetic rats have decreased levels of GSH. The results of the table suggest that diabetes can decrease antioxidant protection in the liver and kidney. This can lead to increased oxidative stress and damage to these organs. The levels of vitamins E and C are significantly lower in the liver and kidney of diabetic rats compared to normal rats. The levels of GSH are also lower in the liver and kidney of diabetic rats compared to normal rats.The results of the table suggest that diabetes can decrease antioxidant protection in the liver and kidney.

DISCUSSION:

The experimental findings indicate that streptozocin (STZ) is a compound that contains a nitrosomethylurea moiety and is preferentially taken up by pancreatic beta-cells through GLUT22. The nitrosomethylurea moiety generates alkylating free radicals, leading to DNA fragmentation and necrosis of beta-cells, resulting in decreased insulin synthesis[11]. However, the poly-ADP-ribose synthetase inhibitor, NA, can prevent the reduction in NAD and proinsulin levels and partially reverse insulin production, thereby preventing the worsening of experimental diabetes induced by beta-cell toxins such as STZ and alloxan. In the context of diabetes, the disease is characterized by stable hyperglycemia, glucose intolerance, and impaired glucose-stimulated insulin secretion both in vivo and in vitro. Aged garlic extract (AGE) has been shown to activate pancreatic beta-cells, leading to insulin production[12]. In this study, we measured the stress levels induced by STZ-NA in diabetic rats. Severe degranulation of damaged beta-cells leads to the development of diabetes. Antioxidants have been found to be beneficial for both diabetic individuals and animals[13]. In diabetic rats, the levels of tissue lipid peroxides (LPO) and oxidative stress markers such as TBARS (thiobarbituric acid reactive substances) and hydroperoxides were significantly increased, while the activities of enzymatic and non-enzymatic antioxidants in plasma and tissues were decreased[14]. The antioxidant glutathione (GSH) was found to be reduced in STZ-induced diabetes, which further promotes LPO. Lipoxygenase peroxides play a role in insulin secretion; however, excessive levels can lead to uncontrolled LPO, cellular infiltration, and islet cell death. Diabetic rats exhibit increased production of tissue lipid peroxides, resulting in elevated TBARS levels.

The antioxidant system in diabetes is impaired, leading to increased LPO. In this study, we observed elevated levels of TBARS and hydroperoxides in the plasma of diabetic rats[15]. However, administration of AGE significantly reduced TBARS and hydroperoxides in diabetic rats, suggesting that AGE may lower blood

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glucose levels by scavenging free radicals and protecting pancreatic islets from STZ-induced damage. The defense against free radicals relies on the presence of antioxidants[16]. In diabetes, antioxidant levels are decreased, thereby increasing the damage caused by free radicals. Superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), and glutathione S-transferase (GST) are enzymes that scavenge damaging reactive oxygen species (ROS) generated during incomplete oxidation processes. SOD and CAT are key enzymes in the elimination of oxygen free radicals. If the activity of antioxidant enzymes decreases, O2 and H2O2 can generate hydroxyl radicals (OH), initiating LPO. SOD protects against oxygen free radicals, while CAT deactivates H2O2, protecting tissues from highly reactive OH radicals[17]. Glycation or inactivation of these enzymes may reduce their activity in diabetes. Antioxidants, whether natural or synthetic, can prevent oxidative damage[18]. The administration of AGE increased the activities of SOD and CAT in diabetic rats compared to the control group. The reactivation of SOD by AGE may enhance the dismutation of O2 and H2O2, which are quickly eliminated by CAT, thus protecting the hepatic and renal tissues of diabetic rats from highly reactive OH and LPO. In the liver and kidney tissues of diabetic rats, the antioxidant enzymes GPx and GST, which scavenge H2O2 and lipid hydroperoxides, were significantly reduced[19]. GPx converts hydroperoxides and reduced glutathione (GSH) to glutathione disulfide (GSSG) and water, with GSH serving as a co-substrate. Reduced activity of GPx and GST can occur due to radical inactivation or glycation in the presence of ROS. Diabetes can also lead to decreased levels of GSH[20]. However, administration of AGE improved the activities of GPx and GST in diabetic rats. Glutathione reductase (GR) is a flavin-containing pyridine nucleotide-disulphideo-reductase that reduces oxidized glutathione (GSSG) to reduced glutathione (GSH). Diabetes is associated with reduced GR activity, suggesting a decrease in GSH production and availability. Glucose-6-phosphate dehydrogenase (G6PD) in the hexose monophosphate (HMP) shunt pathway plays a role in generating NADPH for GR activation. Reduced G6PD activity in diabetes can lead to decreased NADPH and GSH levels. However, AGE treatment increased G6PD activity, NADPH levels, and GR activity in diabetic rats, thereby restoring tissue antioxidant GSH levels[21].

GSH plays a crucial role in protecting cells from oxidative stress. Depletion of GSH can lead to ROS and oxidative stress-induced damage to cell and organelle membranes. GSH is involved in the recycling of vitamin C and acts as a co-substrate for GPx and GST in combating oxygen radicals. STZ-induced diabetic rats showed decreased levels of tissue GSH, which may contribute to increased oxidative damage. However, treatment with AGE resulted in higher levels of plasma and tissue GSH in diabetic rats, indicating a reduction in oxidative damage. The ratio of GSH to GSSG and the quantitation of GSSG reflect the level of oxidative stress in cells and tissues[22]. Under severe oxidative stress, the ratio of GSH to GSSG decreases, and GSSG levels increase. In diabetes, the thiol groups in GSH/GSSG regulate glucose homeostasis by modulating intracellular and membrane redox states. Hyperglycemia can divert glucose to the polyol pathway, depleting NADPH and GSH levels. However, AGE therapy in diabetic rats significantly decreased GSSG levels and increased tissue GSH levels and the GSH/GSSG ratio, indicating a reduction in oxidative stress[23]. Diabetic rats often exhibit deficiencies in vitamins C and E. Vitamin E acts as a physiological antioxidant and stabilizes cell membranes. It inhibits the activity of lipid peroxy radicals, thus protecting cell structures from LPO. Vitamin C eliminates free radicals in both plasma and tissues. Metabolism disorders of vitamin C may contribute to the development of diabetes. Hyperglycemia can impede the absorption of dehydroascorbic acid, the oxidized form of vitamin C[24]. Vitamin C helps to remove harmful hydroxyl radicals. In this study, diabetic rats showed significantly lower levels of plasma and tissue vitamin C and E, which may be attributed to oxidative stress.[25] However, AGE administration directly scavenges free radicals and reduces oxidative stress.

Overall, the findings suggest that administration of aged garlic extract (AGE) has beneficial effects in diabetic rats by reducing oxidative stress, scavenging free radicals, enhancing antioxidant enzyme activities, restoring tissue antioxidants, and improving liver and kidney function. These effects may contribute to the regulation of glucose homeostasis and the protection of pancreatic islets from damage induced by STZ.

CONCLUSION:

In summary, aged garlic extract (AGE) contains beneficial compounds like allixin, selenium, and organosulfur compounds. AGE reduces reactive oxygen species (ROS) levels, enhances antioxidant enzyme activity, lowers lipid peroxidation, and prevents LDL oxidative modification. It inhibits the activity of the oxidant-induced transcription factor NF(kB) and protects against DNA damage, multistep carcinogenesis, ionizing radiation, UV-induced damage, and immunological suppression. AGE has shown potential benefits in improving cognitive ability, memory, and longevity in a mouse model. It also mitigates cardiotoxicity and liver toxicity induced by certain drugs and chemicals. However, further research is needed to explore the full extent of AGE's preventive and protective effects against oxidant-induced illnesses and long-term toxic damage.

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