Effect of Garlic and Aged Black Garlic on Hyperglycemia and Dyslipidemia in Animal Model of Type 2 Diabetes Mellitus

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Abstract

Control of hyperglycemia and dyslipidemia is strongly correlated with decreased risk for cardiovascular disease, the most common and fatal diabetic complication. The purpose of this study is to determine the effects of garlic and aged black garlic on glycemic control and blood lipid profile in animal model of type 2 diabetes. Three week-old db/db mice (C57BL/Ks, n=21) were fed AIN-93G semipurified diet or diet containing 5% freeze-dried garlic or aged black garlic for 7 weeks after 1 week of adaptation. Fasting serum glucose, insulin, triglyceride, total cholesterol, and HDL-cholesterol and blood glycated hemoglobin were measured. Body weight and food intake of garlic and aged black garlic group were not significantly different from those of the control group. Fasting serum glucose and blood glycated hemoglobin levels were significantly decreased and insulin level was significantly increased in garlic group compared with control group (p<0.05). Consumption of aged black garlic significantly decreased homeostasis model assessment for insulin resistance (HOMA-IR) and tended to decrease serum glucose. Garlic consumption significantly decreased total cholesterol, while aged black garlic significantly reduced serum total cholesterol and triglyceride and increased HDL-cholesterol levels. These results suggest that garlic exerts hypoglycemic and hypocholesterolemic effect and aged black garlic improved insulin sensitivity and dyslipidemia in db/db mice.

Key words: diabetes mellitus, garlic, aged black garlic, hyperglycemia, dyslipidemia

INTRODUCTION

Type 2 diabetes mellitus is characterized by chronic hyperglycemia with disturbances of carbohydrate, fat, and protein metabolism resulted from defects in insulin action. Cardiovascular disease (CVD) is a major complication and the leading cause of premature death among patients with type 2 diabetes (1). Controlling blood glucose levels as close to normal and preventing diabetic complications are the major goals in the treatment of diabetes mellitus (2,3). Tight control of hyperglycemia and aggressive treatment of dyslipidemia are associated with the reduced risk for CVD in diabetic patients (4).

Garlic (*Allium sativum* L.) has been known to have health benefits for centuries. Evidence from several investigations has shown that garlic has antibacterial (5,6), anticarcinogenic (7), antidiabetic (8,9), antioxidant (10), and hypolipidemic effects (11,12). The administration of 80% ethanol extract of garlic at dose of 0.5 g/kg decreased serum glucose, total cholesterol, and triglyceride in streptozotocin (STZ)-induced diabetic rats (8). Injection of garlic extract attenuated hypoglycemia and

structural nephropathy progression in STZ-induced diabetic rats (9). It was reported that consumption of diet containing 5% garlic powder showed hypolipidemic effect in rats (13). Thus, garlic could be helpful in treatment of diabetes by exerting hypoglycemic and hypolipidemic effects. However, the beneficial effects of garlic in animal model of type 2 diabetes were not studied.

Recently aged black garlic produced by ageing whole garlic at high temperature (70°C) and high humidity (90% RH) has been available on the market in Korea (14-16). During ageing unstable and highly odorous compounds of fresh garlic including alliin are converted into stable and odorless compounds including S-allyl cysteine, the organo-sulphur compound with potent antioxidant effect (5,17). It was reported that aged black garlic contained increased content of total polyphenol and antioxidant activity compared with garlic (14). Aged black garlic exerted strong hypolipidemic effect in rats fed diet supplemented with cholesterol (18). Therefore, aged black garlic could be beneficial in management of diabetes. However, the effects of aged black garlic on carbohydrate and lipid metabolism in diabetes were not

studied. Therefore, the present study was aimed to investigate the effects of garlic and aged black garlic offered at 5% level of the diet on hyperglycemia and dyslipidemia in animal model of type 2 diabetes mellitus.

MATERIALS AND METHODS

Reagents

Assay kits for glucose, triglyceride, cholesterol, and HDL-cholesterol were purchased from Asan Co. (Seoul, Korea) and a glycated hemoglobin assay kit from BioSystems (Barcelona, Spain). A radioimmunoassay kit for insulin was acquired from Linco Co. (St. Charles, MO, USA). Cornstarch was obtained from Daesang Co. (Seoul, Korea). Casein, L-cystine, mineral mixture, and vitamin mixture were purchased from ICN Pharmaceuticals Inc. (Costa Mesa, CA, USA) and *tert*-Butyl hydroquinone from Fluka Co. (Milwaukee, WI, USA). Sucrose and soybean oil were obtained from Cheiljedang Co. (Seoul, Korea). Alphacel, choline bitartrate, and all other reagent grade chemicals were purchased from Sigma Chemical Co. (St. Louis, MO, USA).

Proximate analyses of garlic and aged black garlic

Garlic was purchased from a local market in Namhaegun and aged black garlic from Injoy Natural Co. (Namhaegun, Korea). Briefly, whole garlic was heated at 55°C and 90% RH for 60 min, at 70°C for 60 min, and then 85°C for 24 hr and fermented at room temperature for 3 weeks. Garlic and aged black garlic were peeled off, freeze-dried, and powdered. Proximate analyses of garlic and aged black garlic were performed according to standard AOAC methods (19).

Animals and diets

Three-week-old male db/db (+/+) C57BL/KsL mice (n=21) were purchased from the Korea Research Institute of Bioscience and Biotechnology (Ochang, Korea). Control group was offered a standard AIN-93G diet, whereas garlic or aged black garlic group were offered the diet containing 5% freeze-dried garlic or aged black garlic *ad libitum* for 7 weeks after 1 week of adaptation, respectively (Table 1). The contents of protein, fat, and dietary fiber of the three diets were the same, respectively. The mice were housed individually in plastic cages and located in a room where temperature ($23 \sim 27^{\circ}$C), humidity ($50 \sim 60$%), and lighting cycle ($0600 \sim 1800$ hr light and $1800 \sim 0600$ hr dark) were controlled. Body weight and food intake were measured three times a week.

Biochemical analyses

After 7-week feeding of the assigned diet, the mice

Table 1. Composition of experimental diets (%)

Ingredient	Group		
	Control	Garlic	Aged black garlic
Cornstarch[1]	39.75	39.30	38.88
Casein[2]	20.00	18.99	19.15
Dextrinized cornstarch[3]	13.20	13.20	13.20
Sucrose[4]	10.00	6.84	6.96
Alphacel[5]	5.00	4.64	4.79
Mineral mixture[6]	3.50	3.50	3.50
Vitamin mixture[7]	1.00	1.00	1.00
L-Cystine[2]	0.30	0.30	0.30
Choline bitartrate[5]	0.25	0.25	0.25
tert-Butylhydroquinone[8]	0.0014	0.0014	0.0014
Soybean oil[4]	7.00	6.99	6.98
Garlic[9]	−	5.00	−
Aged black garlic[9]	−	−	5.00

[1]Daesang Co., Korea.
[2]ICN Pharmaceuticals Inc., USA.
[3]Dyets. Inc., USA.
[4]Cheiljedang Co., Korea.
[5]Sigma Co., USA.
[6]AIN-93G Mineral mixture, ICN Pharmaceuticals, USA.
[7]AIN-93G Vitamin mixture, ICN Pharmaceuticals, USA.
[8]Fluka Co., USA.
[9]Freeze-dried.

were sacrificed by heart puncture after an overnight fast. Blood glycated hemoglobin was measured by the chromatographic method (20) using a commercial assay kit. Blood samples were centrifuged at $3,000 \times g$ for 15 min; serum was removed and frozen at -70°C for further analysis. Serum glucose (21), total cholesterol (22), and HDL-cholesterol (23), and triglyceride (24) were measured by enzymatic methods using commercial assay kits. Serum insulin was measured by radioimmunoassay (25) using a commercial assay kit. Homeostasis model assessment for insulin resistance (HOMA-IR), a biomarker to assess insulin resistance, was calculated by dividing the product of insulin (μU/mL) and glucose (mmol/L) by 22.5 (26). The experiments were performed according to the guidelines of animal experimentation approved by the Animal Resource Center at Inje University, Korea.

Statistical analysis

All values were expressed as mean±standard deviation (SD). All statistical analyses were performed using SAS (version 8.02). Statistical differences among the experimental groups were assessed by one-way ANOVA. Tukey's test was used as a follow-up test and significance was defined at $p < 0.05$.

RESULTS AND DISCUSSION

Proximate composition

Proximate composition of garlic and aged black garlic

Table 2. Proximate composition of garlic and aged black garlic (%)

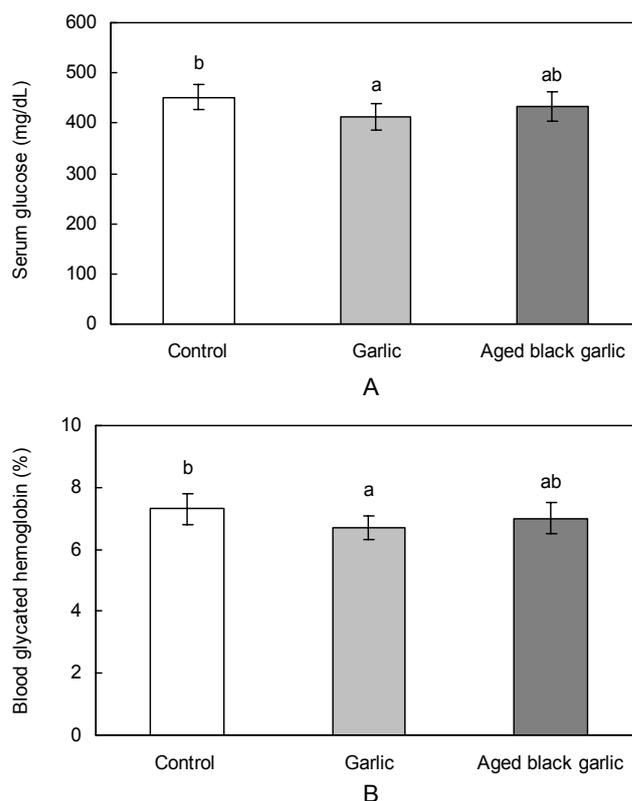|	Garlic[1]	Aged black garlic[1]
Moisture	5.4	13.9
Crude fat	0.3	0.5
Crude protein	20.2	17.0
Crude ash	3.6	3.5
Dietary fiber	7.2	4.3

[1]Freeze-dried.

was shown in Table 2. The content of fat, protein, ash, and dietary fiber of freeze-dried garlic were 0.3%, 20.2%, 3.6% and 7.2%, respectively. Aged black garlic contained 0.5% fat, 17.0% protein, 3.5% ash, and 4.3% dietary fat.

Body weight and food intake

Body weight and food intake of the mice were shown in Table 3. Final body weight of control, garlic, and aged black garlic group were 41.8 ± 1.8, 42.9 ± 1.9, and 41.2 ± 2.5 g, respectively. Food intake of control, garlic, and aged black garlic group were 4.3 ± 0.4, 4.1 ± 0.3, and 4.2 ± 0.6 g/d, respectively. Chronic consumption of garlic and aged black garlic at the level of 5% of the diet did not significantly influence body weight, food intake, and feed efficiency ratio in db/db mice. It was reported that consumption of garlic and aged black garlic at the level of 3% of the diet did not influence body weight and food intake of rats fed diet containing 1% cholesterol (18).

Glycemic control

The effect of garlic and aged black garlic on glycemic control was shown in Fig. 1. Consumption of garlic significantly decreased fasting serum glucose (412.9 ± 25.3 mg/dL) and blood glycated hemoglobin level ($6.7 \pm 0.4\%$) compared with the control group (452.1 ± 25.6 mg/dL and $7.3 \pm 0.5\%$, respectively, $p < 0.05$). The fasting serum glucose level (433.1 ± 28.8 mg/dL) and glycated hemoglobin level ($7.0 \pm 0.5\%$) of aged black garlic group were not significantly different from the control and garlic group. Plasma insulin level of garlic group

Fig. 1. Effect of garlic and aged black garlic on the levels of fasting serum glucose (A) and blood glycated hemoglobin of db/db mice (B). Values are mean $\pm$ SD. Each bar with different letters is significantly different ($p < 0.05$).

(61.3 ± 4.4 μU/mL) was significantly higher than control (54.7 ± 5.0 μU/mL) and aged black garlic group (50.9 ± 4.5 μU/mL, $p < 0.05$, Fig. 2). HOMA-IR of aged black garlic group (54.2 ± 3.6) was significantly lower than control (60.9 ± 4.5) and garlic group (62.4 ± 4.4, $p < 0.05$).

The results of this study showed that garlic increased serum insulin levels by 12.1% and reduced glucose by 8.7% and glycated hemoglobin level by 4.1%. Since most of antidiabetic medications could have side effects (27), many studies have been conducted to identify natural substances that show potent hypoglycemic activity with fewer side effects (28-31). *Eucommia ulmoides* Oliver

Table 3. Body weight, food intake, and feed efficiency ratio of the animals

	Group		
	Control	Garlic	Aged black garlic
Initial body weight (g)	20.8 ± 1.5^{ns}	21.1 ± 1.2	20.7 ± 1.7
Final body weight (g)	41.8 ± 1.8^{ns}	42.9 ± 1.9	41.2 ± 2.5
Body weight gain (g/d)	0.43 ± 0.06^{ns}	0.45 ± 0.06	0.42 ± 0.06
Food intake (g/d)	4.3 ± 0.4^{ns}	4.1 ± 0.3	4.2 ± 0.6
Feed efficiency ratio (%)[1]	10.2 ± 2.2^{ns}	10.9 ± 1.2	10.1 ± 2.7

Values represent mean $\pm$ SD (n=7). ^{ns}Not significant.
[1]Feed efficiency ratio (%)=(body weight gain (g/d)/food intake (g/d))$\times 100$.
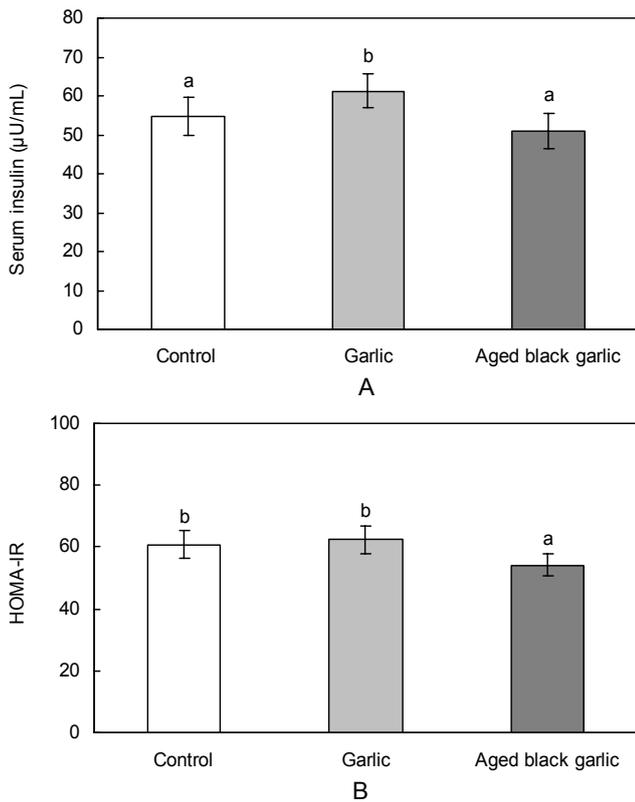
Fig. 2. Effect of garlic and aged black garlic on the levels of serum insulin (A) and HOMA-IR (B) of db/db mice. Values are mean±SD. Each bar with different letters is significantly different (p<0.05). Homeostasis model assessment for insulin resistance (HOMA-IR) was calculated by dividing the product of insulin (μU/mL) and glucose (mmol/L) by 22.5.

(Du-zhong) leaf (28,29), touchi extract (30), and *Commelina communis* (31) showed hypoglycemic activity in animal model of diabetes. Consumption of Du- zhong leaf extract for 6 weeks decreased blood glucose by 18.4% in db/db mice. Consumption of extract of touchi, fermented soybean product at the level of 0.4% of the diet for 60 days reduced blood glucose by 23.7% in KKA[y] mice. Touchi extract has been approved as a health/functional food with hypoglycemic effect by the Korean Food and Drug Administration (32). In our study, garlic powder showed mild hypoglycemic effect in db/db mice. Eidi et al. (8) reported that garlic showed hypoglycemic effect by increasing insulin secretion in STZ-induced diabetic rat. Garlic could attenuate hyperglycemia by stimulating insulin secretion in both type 1 and 2 diabetic animals. It was suggested that thiosulfinate allicin produced from alliin when garlic is crushed, cut or chewed could be the active compound to exert hypoglycemic effect by stimulating pancreatic β-cell (33). Since tight control of blood glucose is one of the major goals for diabetes treatment (2), consumption of garlic could be beneficial in treatment of diabetes.

However, there were no previous reports about the effect of aged black garlic on glycemic control in type 2 diabetes. Our data indicated that aged black garlic supplemented at the level of 5% of diet for 7 weeks did not significantly influence glucose and glycated hemoglobin levels in db/db mice. It was reported that the content of S-allyl cysteine increased, while the content of alliin decreased during ageing of garlic (17). Shin and Ihm (34) reported S-allyl cysteine administered orally at the level of 100 mg/rat for 8 weeks reduced plasma glucose by 12.9% and glycated hemoglobin level by 11.3% in STZ-induced diabetic rats. Aged garlic extract prepared from ageing of garlic at room temperature for 20 months contained approximately 1,000 μg/g S-allyl cysteine, while raw garlic contained 20 μg/g (35). In this study whole garlic was aged for 3 weeks after heating at 55°C for 60 min, at 70°C for 60 min, and then 85°C for 24 hr to produce aged black garlic. Jang et al. (14) reported that aged black garlic could be produced by ageing whole garlic at 70°C for 240 hr and then 35°C for 72 hr. Therefore, the concentration of s-allyl cysteine of aged black garlic could be less than that of aged garlic extract. In this study aged black garlic given at 5% level of diet may not contain enough amount of s-allyl cysteine to exert hypoglycemic effect. Further study to quantify s-allyl cysteine of aged products of garlic with different ageing condition could be necessary.

However, aged black garlic alleviated insulin resistance in db/db mice, obese-diabetic animals with insulin resistance. Insulin resistance is an important initiating pathogenic mechanism of type 2 diabetes (36). Therefore, improvement of insulin resistance by aged black garlic could be beneficial in prevention and management of type 2 diabetes. Further study to investigate the effects of feeding various levels of aged black garlic on glycemic control of diabetic animals for longer period of time could be necessary.

Serum lipid profile

Fig. 3. showed the effect of garlic and aged black garlic on serum lipid profile. Consumption of garlic significantly decreased serum total cholesterol levels (146.0±7.9 mg/dL, p<0.05) but did not decrease triglyceride (148.6±12.5 mg/dL) and HDL-cholesterol levels (65.7±5.0 mg/dL) compared with the control group (159.6±9.0 mg/dL, 163.4±15.9 mg/dL, and 58.6±5.3 mg/dL, respectively). Aged black garlic significantly decreased total cholesterol (142.9±9.3 mg/dL) and triglyceride (139.0±19.0 mg/dL) and increased HDL-cholesterol levels (68.7±7.4 mg/dL) compared with the control group (p<0.05). Serum cholesterol, triglyceride, and HDL-cholesterol levels of aged black garlic group were
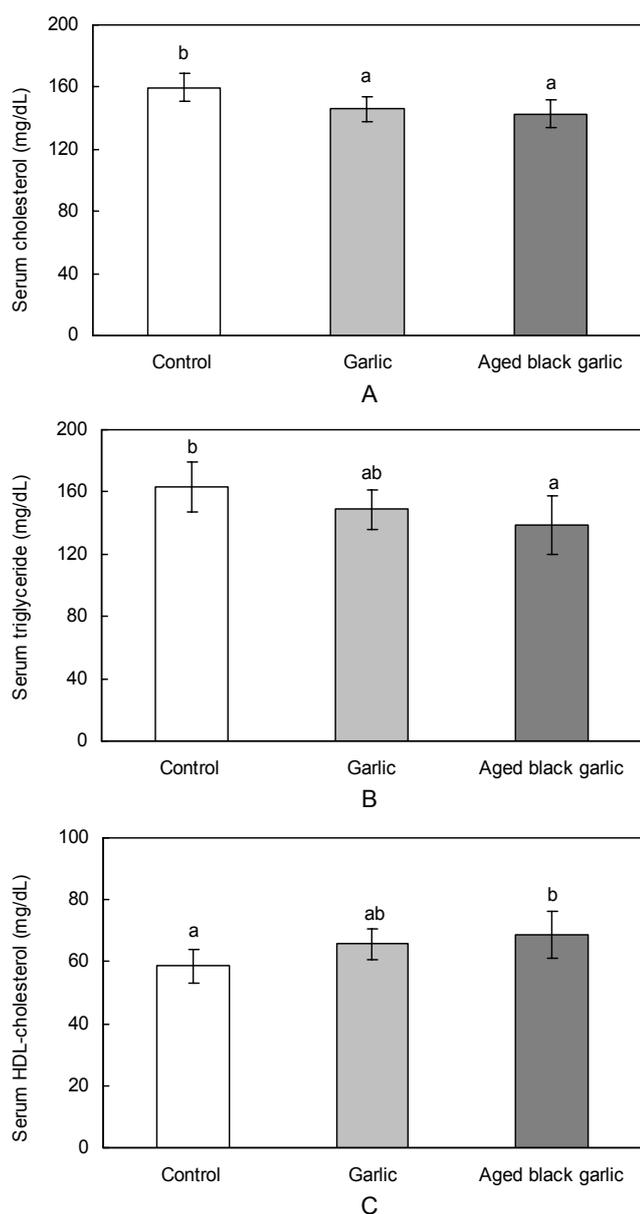
Fig. 3. Effect of garlic and aged black garlic on the levels of serum total cholesterol (A), triglyceride (B), and HDL-cholesterol of db/db mice (C). Values are mean±SD. Each bar with different letters is significantly different ($p<0.05$).

not significantly different from garlic group.

The hypolipidemic effect of garlic has been the subject of controversy. Kang et al. (18) reported that garlic powder reduced serum triglyceride and total cholesterol in rats fed diet containing 1% cholesterol. It was suggested that allicin was the active compound responsible for hypolipidemic effect (5,37). However, Ismail et al. (38) demonstrated that garlic powder resulted in only a significant decrease in total serum cholesterol but not the triglyceride levels. Aouadi et al. also reported that fresh garlic supplementation at the level of 10% of the diet improved hypercholesterolemia but not hypertriglyc-

eridemia in rats fed high cholesterol diet (11). In this study garlic powder significantly decreased total cholesterol without significant change in triglyceride levels in db/db mice. However, aged black garlic significantly decreased total cholesterol and triglyceride levels.

This study demonstrated that garlic tended to increase HDL-cholesterol, while aged black garlic significantly increased HDL-cholesterol levels in db/db mice. Our data are in very close agreement with the previous report by Shin and Kim (39), who reported that consumption of diet containing 5% garlic powder did not influence HDL-cholesterol levels in adult rats. It was also reported that aged black garlic was more effective than garlic in increasing HDL-cholesterol levels in cholesterol-fed rats (18). Elevated serum triglyceride and decreased HDL-cholesterol are major characteristics of diabetic dyslipidemia and improvement of dylipidemia leads to a decrease in the risk of micro- and macrovascular complications of diabetes (2,3). Therefore, aged black garlic could be more beneficial than garlic in improvement of cardiovascular complications of diabetes. Further study could be necessary to identify the active components of aged black garlic with hypolipidemic effects.

Jang et al. (14) reported that the total polyphenol content of aged black garlic was increased (10.00 mg/g), although the content of polyphenol compounds of garlic was not high (3.67 mg/g). It was demonstrated that S-allyl cysteine (5,17) and polyphenol compounds exert strong antioxidant effect (40). Since hyperglycemia in diabetes leads to increased formation of reactive oxygen species (41) and the resulting oxidative stress plays a major role in the progression of diabetes and diabetic complications (42), aged garlic could be beneficial in improvement of diabetes. It could be necessary to investigate the effective dosage of aged black garlic to exert antioxidant effect in animal model of diabetes.

In conclusion, garlic decreased serum glucose and increased insulin levles, whereas aged black garlic improved insulin sensitivity in animal model of type 2 diabetes. Garlic reduced serum total cholesterol, while aged black garlic reduced serum total cholesterol and triglyceride and increased HDL-cholesterol. Therefore, both garlic and aged black could be beneficial in treatment of type 2 diabetes.

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