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Anti-Diabetic Effect of Black Ginseng in C57BLKS/J-*db/db* Mice

Shin-Jung Kang and †Ae-Jung Kim*

Dept. of Medicine Resources, Graduate School of Jungboo University, Choongnam 312-702, Korea
**The Graduate School of Alternative Medicine, Kyonggi University, Seoul 120-837, Korea*

C57BLKS/J-*db/db* 마우스에서 흑삼의 항당뇨 효과

강 신 정 · †김 애 정*

중부대학교 한약자원학과, *경기대학교 대체의학대학원 대체의학과

국문요약

본 연구는 흑삼의 항당뇨 효과를 알아보고자 4그룹(정상군, 당뇨 쥐, 당뇨 쥐에게 백삼을 투여한 군, 당뇨 쥐에게 흑삼을 투여한 군)으로 나누어 6주간 실시하였다. 6주 후 식품섭취량, 체중 증가량을 비교하였는데, 식품섭취량, 체중 증가량에는 그룹 간에 유의적인 차이가 나타나지 않았으나, OGTT(oral glucose tolerance test)와 IPITT(intraperitoneal insulin tolerance test) 경우는 흑삼 투여군에서 긍정적인 결과를 나타내었다. 또한 혈청 포도당과 인슐린농도에 미친 영향을 비교, 분석한 결과, 흑삼 투여군에서 공복 시 혈당, 혈청 포도당, 인슐린 농도가 유의적으로 감소하였다. 이 결과를 미루어 볼 때 흑삼이 백삼에 비해 당뇨를 치료하는데 더 효과적일 것으로 판단된다.

Key words: C57BLKS/J-*db/db* mice, OGTT, IPITT, blood insulin, blood glucose, black ginseng

INTRODUCTION

Diabetes mellitus was generally classified into two major categories: type 1 diabetes (insulin-dependent diabetes mellitus, or IDDM) and type 2 diabetes (non-insulin-dependent diabetes mellitus, or NIDDM). Among diabetes mellitus patients, 85～90% is suffering from type 2 diabetes (Attele et al. 2002), which is an increasing health problem worldwide, and the most common type of diabetes (Alberti & Zimmer 1998). Although the pathogenesis of type 2 diabetes remains less than completely understood, evidence is accumulating to support the notion that type 2 diabetes is the consequence of abnormalities in glucose metabolism (Zhang et al. 2004). Additionally, central obesity and insulin resistance, which can lead to hyperinsulemia, are known risk factors for diabetes (Lenharg & Gottschalk 2002). Insulin resistance plays a primary role in the development of type 2 diabetes (DeFronzi RA 1988; Peter et al. 2003). Therefore hyperinsulinemia should considered major intervention target for the reduction of NIDDM incidence. Although NIDDM is known to be inextripable, it has become possible for the patients to control their blood glucose level by the recent study which has brought about a considerable progress on the synthetic drugs (Kato & Miura 1994).

Despite the considerable number of available preventive strategies and medical treatments, 300 million people worldwide are expected to have developed NIDDM by 2025 (Scheen AJ 2000; Seidell JC 2000). As a consequence, many are turning to alternative therapies, including herbal medicines. In particular, plants have been utilized as traditional medicine for the treatment of diabetes, and some such treatments have been demonstrated to ameliorate certain diabetic complications, with or without a hypoglycemic effect (Neef et al. 1995). Several hundreds of species have already been reported to exert anti-diabetic effects, but only a few of these have been investigated in any rigorous way

† Corresponding author: Ae-Jung Kim, The Graduate School of Alternative Medicine, Kyonggi University, Seoul 120-837, Korea. Tel: +82-2-390-5044, Fax: +82-2-390-5078, E-mail: kaj419@kgu.ac.kr

(Ivorra et al. 1989; Noel et al. 1997).

Korean ginseng has been traditionally utilized as an anti-diabetic remedy for many years in Asian countries, most notably Korea and China. In Korea, three types of ginsengs (white, red and black) are three. Among them several studies about white and red ginseng have suggested that white or red ginseng intake may possibly control postprandial hyperglycemia in both healthy and diabetic individuals (Vuksan et al. 2000; Soonthornpun et al. 1999; Turner RC 1998; Park et al. 2003). However, the possible anti-diabetic effects of black ginseng have yet to be rigorously evaluated.

As the brief description of black ginseng, it is a relatively new product with black color in Korea, which color is manufactured via successive 9 cycle processes of steaming and drying treatment (Lee et al. 2006). The black ginseng shows a marked difference on the ratios of major bioactive components, as kinds and contents of ginsenosides by the comparison with white ginseng (Hasegawa et al. 1997a; Yun TK 2003). By several studies, black ginseng has been reported to exhibit anti- carcinogenic, anti-stress, and antioxidant effects in humans and animals (Kang et al. 2006). Thus, we attempted herein to determine whether black ginseng exerts anti-diabetic effect, specifically as compared to white ginseng the anti-diabetic effect of which have already been elucidated in a number of previous studies (Vuksan et al. 2000; Soonthornpun et al. 1999; Turner RC 1998). A new ginseng product, namely black ginseng contains a large number of ginsenoside Rg3 (10.94 ㎎/g) than that of white ginseng (none) or red ginseng (0.80 ㎎/g) (Kim & Kang 2009).

In short, the principal objective of this study was to determine which type of ginseng (white or black) has more effective on the anti-diabetic effect in C57BL/KSJ-*db/db* mice, a type 2 diabetic mice model.

MATERIALS AND METHODS

1. Manufacturing of Black Ginseng

Five-years-old flesh Korean ginseng was purchased from Keumsan Oriental Medicine Market Complex in Choongnam Province, Korea in 2010. White ginseng sample (WG) was prepared that the fresh ginseng was dried (FDI-150, Labhouse, Gyeonggi, Korea) at 50 to 55℃. And then it was pulverized to powder below 100 mesh and used as white ginseng sample. Black ginseng sample (BG) was produced by successive 9 times-steaming and drying the flesh ginseng in the condition of 80℃ for 2 hrs for steam treatment and 50 to 55℃ for 2 or 3 hrs for dry treatment ,and then it was pulverized in less than 100 mesh, prior to vacuum-freezing dry (Freezone 6, Labconco, Kansas, USA).

2. Animals and Diets

Six weeks-old, male obese diabetic C57BLKS/J-*db/db* mice in genetic background, and their lean non-diabetic heterogeneous littermates, *db/m* mice, as vehicle were purchased from Jungang Experimental Animal Co. (Seocho-ku, Seoul, Korea) and maintained under standard light (12 h light/dark cycle), temperature (22±2℃) and humidity (50±20%) conditions. The animals were permitted to acclimate to the laboratory environment for 4 weeks. And ten-weeks-old mice male *db/db* mice were administrated with once daily 300 ㎎/㎏ body weight of each of WG and BG for 6 weeks, *db/m* mice as normal group and *db/db* mice as diabetic positive group were fed without treatment of WG and BG (Table 1). The animals were provided with pelletized commercial chow(Purina Korea, Inc., Korea) and distilled water *ad libitum*.

The two types of materials (WG and BG) were intraperitoneally administered at a concentration of 300 ㎎/㎏ body weight using

Table 1. Experimental design

Groups	Administration amount (㎎/㎏)	Solution	Administration concentration (㎎/㎏)	Mouse number
Normal[1)]	10	Sterilized water	0	*db*/m 8
Positive[2)]	10		0	*db/db* 8
WG[3)]	10		300	*db/db* 8
BG[4)]	10		300	*db/db* 8

[1)] Normal group: *db*/m type-nondiabetic hetero mice fed only with sterilized water without experimental samples,
[2)] Positive group: diabetic *db/db* homo mice fed only with sterilized water without experimental samples,
[3)] WG: Test group of diabetic *db/db* homo mice fed with the concentration of 300 ㎎ of white ginseng/㎏ body weight,
[4)] BG: Test group of diabetic *db/db* homo mice fed with the concentration of 300 ㎎ of black ginseng/㎏ body weight.

sonde once per day for 6 weeks. All procedures involving animals were approved by Experimental Animal Care Committee of Chungbuk University, Chungbuk, Korea.

3. Food Consumption and Change of Body Weight

Food consumption and body weight change were measured at weekly intervals at 9:00 am.

4. Oral Glucose Tolerance Test (OGTT), and Intraperitoneal Insulin Tolerance Test (IPITT)

Oral glucose tolerance test and intraperitoneal insulin tolerance test were performed after 12 h fasting on the 5 th weeks. Mice were administrated orally with glucose (1.5 g/㎏ body weight) and injected with intraperitoneally insulin (1 units/㎏ body weight). Blood glucose levels were determined from the tail vein using a glucometer (All Medicus, Seoul, Korea) at 0, 30, 60, and 120 min after the glucose administration orally and at 0, 30, 60, 120 min after the insulin injection intraperitoneally.

5. Blood Glucose and Insulin Levels

At the end of the experimental period, the mice were anesthetized with ether after 12 h of fasting, and the blood samples were obtained in heparin-coated tubes and centrifuged at 3,000 rpm for 15 min at 4℃ from the inferior vena cava in order to determine the serum glucose and insulin via ELISA method using a ELISA kit (Cat. No. AKRIN-011H, Shibayagi Co. Ltd., Japan), respectively.

6. Statistical Analysis

Results were expressed as mean±SD of 8 mice per group and statistical significance was assessed via one-way analysis of variance (ANOVA) and Duncan's multiple range test using SAS software (SAS analysis system, ver. 8.1). Values were considered statistically significant at $p<0.05$.

RESULTS

1. Food Consumption and Body Weight Gain

The food consumption and body weight gain were shown in Table 2 and 3. Food consumption of all diabetic groups were significantly higher than that of normal control group from 2 weeks to 6 weeks. But both WG and BG treatment groups were not shown significant differences on food consumption as compared to the positive control group during all the experimental period (Table 2).

The body weight gain of all diabetic groups were significantly lower than that of normal control group, but among diabetic groups there were no significant differences (Table 3).

2. Oral Glucose Tolerance Test (OGTT), and Intraperitoneal Insulin Tolerance Test (IPITT) measurement

An oral glucose tolerance test (OGTT) and an intraperitoneal insulin tolerance test (IPITT) were performed to determine the effects of WG and BG administration at five weeks of the experiment and the results were presented in Table 4. The blood glucose level did not significantly differ between WG and BG group up to 60 min, however, at 90 min after the glucose load, glucose level was significantly lower in the WG group not BG group than the positive control group even thought two type of treatment groups failed to return to the baseline after 120 min. In case of an IPITT, both WG and BG group didn't show a rapid removal of blood glucose compared to the normal control group. But the BG group was shown a rapid removal of blood glucose compared with the WG group. The BG group exhibited the most

Table 2. Food consumption of diabetic *db/db* mice treated with test materials(WG and BG) for 6 weeks (g)

Periods	Normal control[1)]	C57BLKS/J-*db/db* mice		
		Positive control[2)]	WG[3)]	BG[4)]
1 week	4.09±0.38[5)NS6)]	5.15±0.16	5.18±0.31	5.51±1.01
2 weeks	3.22±0.13[NS]	4.01±1.03	4.39±0.47	4.60±0.98
4 weeks	4.20±0.41[b]	6.72±0.26[a]	7.10±0.97[a]	6.70±0.97[a]
6 weeks	4.48±0.35[b]	7.37±0.56[a]	7.48±0.86[a]	7.49±0.83[a]

[1)] Normal group: *db*/m type-nondiabetic hetero mice fed only with sterilized water without experimental samples,
[2)] Positive group: diabetic *db/db* homo mice fed only with sterilized water without experimental samples,
[3)] WG: Test group of diabetic *db/db* homo mice fed with the concentration of 300 ㎎ of white ginseng/㎏ body weight,
[4)] BG: Test group of diabetic *db/db* homo mice fed with the concentration of 300 ㎎ of black ginseng/㎏ body weight,
[5)] Mean±SD, [6)] Means in the same row not sharing a common superscript are significantly different($p<0.05$) between groups.

Table 3. Body weight of diabetic *db/db* mice treated with test materials(RG and BG) for 6 weeks (g)

Periods	Normal control[1)]	C57BLKS/J-*db/db* mice		
		Positive control[2)]	WG[3)]	BG[4)]
0 week	23.08±0.99[5)b)6)]	31.53±4.33[a]	31.82±5.61[a]	31.69±6.23[a]
2 weeks	23.73±0.84[b]	30.20±4.41[a]	31.61±6.26[a]	31.10±7.36[a]
4 weeks	25.50±1.12[b]	31.44±4.54[a]	32.72±6.54[a]	32.62±7.37[a]
6 weeks	26.58±0.93[b]	34.06±5.71[a]	34.50±7.22[a]	34.25±8.37[b]
Weight gain	3.50±0.45[a]	2.53±0.43[b]	2.68±0.39[b]	2.56±0.28[c]

1) Normal group: *db*/m type-nondiabetic hetero mice fed only with sterilized water without experimental samples,
2) Positive group: diabetic *db/db* homo mice fed only with sterilized water without experimental samples,
3) WG: Test group of diabetic *db/db* homo mice fed with the concentration of 300 ㎎ of white ginseng/㎏ body weight,
4) BG: Test group of diabetic *db/db* homo mice fed with the concentration of 300 ㎎ of black ginseng/㎏ body weight,
5) Mean±S.D., 6) Means in the same row not sharing a common superscript are significantly different(p<0.05) between groups.

Table 4. Oral GTT of diabetic *db/db* mice treated with test materials(WG and BG)

Groups	0	30	60	90	120 min
Normal	80.75± 7.54[1)b2)]	216.25± 39.38[b]	152.00± 15.38[b]	124.50± 13.48[c]	106.50± 8.89[c]
Positive	292.75±94.36[a]	820.50± 69.53[a]	764.25±201.82[a]	651.00±138.22[a]	607.75±123.49[a]
WG	292.25±35.80[a]	723.50±129.27[ab]	680.75± 91.20[ab]	608.00±154.10[ab]	584.50±145.03[ab]
BG	303.75±91.07[a]	732.50± 79.99[ab]	647.25±121.68[ab]	534.25±101.60[b]	461.50±129.64[b]

1) Normal group: *db*/m type-nondiabetic hetero mice fed only with sterilized water without experimental samples,
2) Positive group: diabetic *db/db* homo mice fed only with sterilized water without experimental samples,
3) WG: Test group of diabetic *db/db* homo mice fed with the concentration of 300 ㎎ of white ginseng/㎏ body weight,
4) BG: Test group of diabetic *db/db* homo mice fed with the concentration of 300 ㎎ of black ginseng/㎏ body weight,
5) Mean±S.D., 6) Means in the same row not sharing a common superscript are significantly different(p<0.05) between groups.

Table 5. IPITT of diabetic *db/db* mice treated with test materials(WG and BG)

Groups	0	30	60	90	120 min
Normal	78.25± 7.50[1)b2)]	77.00± 13.59[b]	53.25±13.50[c]	61.50± 10.25[b]	78.75± 17.00[c]
Positive	253.50±76.09[a]	424.75± 79.61[a]	327.00±44.02[a]	264.50± 73.02[a]	309.75±116.79[a]
WG	248.50±84.60[a]	399.00±206.90[ab]	333.25±86.85[a]	287.75±112.16[a]	300.00± 75.10[a]
BG	241.50±61.56[a]	380.75± 96.83[ab]	284.75±79.11[ab]	256.25± 76.54[a]	264.75± 59.03[ab]

1) Normal group: *db*/m type-nondiabetic hetero mice fed only with sterilized water without experimental samples,
2) Positive group: diabetic *db/db* homo mice fed only with sterilized water without experimental samples,
3) WG: Test group of diabetic *db/db* homo mice fed with the concentration of 300 ㎎ of white ginseng/㎏ body weight,
4) BG: Test group of diabetic *db/db* homo mice fed with the concentration of 300 ㎎ of black ginseng/㎏ body weight,
5) Mean±S.D., 6) Means in the same row not sharing a common superscript are significantly different(p<0.05) between groups.

efficient removal of blood glucose over the entire period during the IPITT in diabetic groups (Table 5).

3. Blood Glucose and Insulin Levels Measurement

At the end of the experimental period, the serum glucose and insulin were shown in Table 6. BG treatment group showed better suppressive effect against increasing blood insulin (p<0.05) and fasting blood glucose level (p<0.05) than that of WG treatment group. WG and BG exhibited anti-diabetic effect on *db/db* mice, dropping 22.2% and 34.3% of blood glucose level, respectively calculated by Eq. 1. It was concluded that BG has better anti-diabetic activity than that of WG.

$$\text{Hypoglycemic activity}(\%) = \frac{\text{Glucose level of positive control group} - \text{Glucose level of WG or BG treatment group}}{\text{Glucose level of positive control group}} \times 100$$

Table 6. Serum glucose and insulin levels of diabetic *db/db* mice treated with test materials(WG and BG)

Groups	Serum glucose(㎎/㎗)	Serum insulin(㎎/㎗)
Normal	198.25±17.50[1)b2)]	1.80±0.25[c]
Positive	8,253.50±76.09[a]	8.50±0.22[a]
WG	648.50±84.60[ab]	5.75±0.16[ab]
BG	541.50±61.56[ab]	3.25±0.54[a]

[1)] Normal group: *db*/m type-nondiabetic hetero mice fed only with sterilized water without experimental samples,
[2)] Positive group: diabetic *db/db* homo mice fed only with sterilized water without experimental samples,
[3)] WG: Test group of diabetic *db/db* homo mice fed with the concentration of 300 ㎎ of white ginseng/㎏ body weight,
[4)] BG: Test group of diabetic *db/db* homo mice fed with the concentration of 300 ㎎ of black ginseng/㎏ body weight,
[5)] Mean±S.D.,
[6)] Means in the same row not sharing a common superscript are significantly different(p<0.05) between groups.

DISCUSSION

According to the World Health Organization, approximately 171 million people worldwide suffered from diabetes in the year 2000. This figure will be predicted to double by 2030 (Wild et al. 2004). All of the currently available pharmacological agents used for the treatment of type 2 diabetes are limited in several ways, most notably in their adverse effects and high secondary failure rates. Owing to these factors, interests been mounting in complementary and alternative approaches, and specifically in the therapeutic use of natural products for diabetes, especially those derived from plants that evidence anti-hypoglycemic activities (Xie et al. 2002a; Xie et al. 2002b). Several studies have suggested that red ginseng intake may possibly control postprandial hyperglycemia in both healthy and diabetic individuals (Vuksan et al. 2000; Soonthornpun et al. 1999; Turner RC 1998). Recently black ginseng, a relatively new product in Korea, is processed by steaming at approximately 100℃ and drying via 9 cycles of steam treatment (Lee et al. 2006). Because of this high-temperature steaming and drying, the ratio of ginsenosides are altered (Hasegawa et al. 1997a; Yun TK 2003).

Fortunately a new ginseng product, namely black ginseng contains a large number of ginsenoside Rg3 (10.94 ㎎/g) than that of white ginseng (none) or red ginseng (0.80 ㎎/g) (Kim & Kang 2009). Ginsenoside Rg3 is currently sought after for their bioactive properties such as anti-tumor, drug-resistance and anti-diabetes (Kim et al. 2003; Keum et al. 2003; Kim & Kang 2009). Black ginseng, but not commonly used white or red ginseng, was evaluated. So, this study was designed for the possible anti-diabetic effects of black ginseng have yet to be rigorously evaluated compared to the white ginseng.

In this study, we measured an oral glucose tolerance test (OGTT) and an IPITT to determine the effects of WG and BG administration at five weeks of the experiment (Table 4 and 5). We observed that BG treatment progressively reduced blood glucose level compared to the positive diabetic group at 90 min after the glucose load even thought two type of treatment groups failed to return to the baseline after 120 min. In case of an IPITT, both WG and BG group didn't show a rapid removal of blood glucose compared to the positive control group. But the BG group showed a rapid removal of blood glucose compared to the WG group. Our results clearly indicate that the BG treatment exhibited the most efficient removal of blood glucose over the entire period during the OGTT and IPITT.

Insulin resistance and obesity are crucial predictors of NIDDM development. Epidemiological studies have indicated that insulin resistance is associated with hyperglycemia (D' Agostino et al. 2004). Thus, the management of hyperinsulinemia and hyperglycemia is critical for the prevention of NIDDM. Pan et al. (1986) has demonstrated that red ginseng effectively lowers blood glucose levels. As type 2 diabetes and insulin resistance are both commonly associated with hyperglycemia, it is important to evaluate the effects of putative anti-diabetic medications (Pi-Sunyer FX 2002).

At the end of the experimental period, the serum glucose and insulin were measured (Table 6). BG treatment group showed better suppressive effect against increasing blood insulin (p<0.05) and fasting blood glucose level (p<0.05) than that of WG treatment group. WG and BG exhibited anti-diabetic effect on *db/db* mice, dropping 22.2% and 34.3% of blood glucose level, respectively calculated by Eq. 1. It was concluded that BG has better anti-diabetic activity than that of WG.

In the present study, we observed that BG has significant anti-hyperglycemic effect in *db/db* diabetic mice. Although positive effects have been shown in this animal model, *db/db* diabetic mice are not miniaturized replicas of the human disease. Thus, caution should be taken when we use our study data to extrapolate certain defined aspects of human type-2 diabetes. Nonetheless, it seems considerably promising and tempting to suggest that if these data can be validated in future clinical trials, BG may offer has complementary potency for widespread use

in treating diabetes compared to the WG.

SUMMARY AND CONCLUSION

This study was designed for the comparison of anti-diabetic effect between white (WG) and black ginseng (BG) in C57BLKS/J-*db/db* mice. Six-weeks-old mice male *db/db* mice were administrated with once daily 300 ㎎/㎏ of each of WG and BG for 6 weeks, *db/m* mice as normal group and *db/db* mice as diabetic positive group were fed without treatment of WG and BG. For finding out anti-diabetic effect, food consumption, body weight gain, oral glucose tolerance test (OGTT), intraperitoneal insulin tolerance test (IPITT) and blood level of glucose and insulin were examined. The results were summarized by comparing the results getting from *db/db* mice administrating WG and BG with those of diabetic positive group for 6 weeks. BG treatment group showed more significant differences on fasting blood glucose, suppression level against increasing blood insulin compared with that of WG group. From above results, BG has better anti-diabetic activity than that of WG.

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