Antidiabetic effect of an extract of nutricultured *Brassica napus* containing vanadium from a Jeju water concentrate

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Abstract The purpose of this study was to determine the antidiabetic effect of an extract of nutricultured *Brassica napus* containing vanadium (BECV). The BECV was prepared following nutriculture of *B. napus* with a Jeju water vanadium concentrate for 7 day. The BECV was administered to *db/db* mice for 8 weeks at different dosages (0.028, 0.14, and 0.7 µg/kg; as vanadium concentration in BECV). After 8 weeks, the BECV results showed mouse blood glucose concentrations to significantly decrease, in a dose-dependent manner, compared with the results for control mice. In addition, the concentrations of triglyceride, total cholesterol, and glycated hemoglobin were significantly lower after 8 weeks of administration of 0.7 µg/kg BECV. Therefore, the BECV may have protective effects against type 2 diabetes.

Keywords Vanadium · *Brassica napus* extract · Antidiabetic effect · *db/db* mouse

Introduction

Diabetes mellitus is a serious metabolic disorder of blood glucose regulation, and it is considered a chronic diseases caused by an inherited or acquired insulin deficiency

disorder that involves destruction of the pancreas and ineffectiveness of the insulin produced. The diabetes-associated hyperglycemia may be due to autoimmune destruction of the insulin-secreting cells of the pancreas (type 1 diabetes mellitus) or it may result from a problem in the responsiveness of tissues to insulin and insufficient insulin utilization, known as insulin resistance (type 2 diabetes mellitus). The most prevalent form is type 2 diabetes mellitus, which is a major problem in today's world and constitutes nearly 95% of the diabetic population. In modern medicine, no satisfactorily effective therapy is available to cure diabetes mellitus (Ghosh and Suryawan-shi, 2001). There is an increasing demand by patients to use natural products with antidiabetic activity due to unwanted side effects associated with the use of insulin and oral hypoglycemic agents (Rao et al., 2001). For a long time, plants, such as *Abies pindrow* (Morinda), *Acacia arabica* (Babool), *Bixa orellana* (Annotta), *Boerhaavia diffusa* (Punamava), *Capsicum frutescens* (Mirch), and *Eucalyptus globulus* (Eucalyptus) (Patel et al., 2012), have been important sources of medicines having insulin mimetic or insulin secretory activity. It has been shown that such plants have hypoglycemic properties and can be used to treat various types of secondary complications of diabetes mellitus.

However, more investigations must be performed to elucidate the exact mechanism of action of medicinal plants with antidiabetic effects. Typically, it is believed that plant-based medicinal products are safe, but many plant materials are unsafe for humans; thus, toxicity studies into such plants should be undertaken before suggesting consumption of some plant materials or products.

Vanadium is a trace element of ubiquitous distribution that constitutes about 0.02% of the earth's crust. It occurs

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at extremely low concentrations in mammalian tissues (0.014–7.2 μM) with an estimated amount of 100–200 μg in humans (Bhuiyan and Fukunaga, 2009). Various compounds that include vanadium have been demonstrated to improve hyperglycemia and aberrant glucose homeostasis in animal models of type 1 and type 2 diabetes mellitus (Srivastava, 1995). The protective effect on streptozotocin-induced diabetic rats (type 1 diabetes mellitus model) was demonstrated for sodium orthovanadate (SOV), sodium metavanadate (NaVO_3), and vanadyl sulfate ($\text{VOSO}_4 \cdot 3\text{H}_2\text{O}/4\text{H}_2\text{O}$) (Brichard et al., 1991; Heyliger et al., 1985; McNeill et al., 1992; Posner et al., 1994; Poucheret et al., 1998; Shisheva et al., 1994). In most of these studies, vanadium salts were administered orally through drinking water, and a glucose-lowering effect was observed within 2–4 days after initiation of treatment. The dose of vanadium salts required to exert a maximum glucose-lowering action varied among studies, but a median concentration of 0.5 mg/mL in drinking water appeared to be sufficient. In studies on type 2 diabetes mellitus models, such as *fafa* Zucker rat, *db/db* mouse, and *ob/ob* mouse, SOV has been shown to improve glucose homeostasis (Brichard et al., 1989; Meyerovitch et al., 1991; Pugazhenthii et al., 1991).

Despite their impressive antidiabetic activity, vanadium compounds have been associated with several toxic effects (Domingo et al., 1995). The most common toxic effects are diarrhea, decreased fluid and food uptake, dehydration, and reduced body weight gain, which can, however, be corrected by adding NaCl to drinking water, adjusting the pH of the solution to neutrality, and by gradually increasing the dose of vanadium (Bendayan and Gingras, 1989; Bollen et al., 1990; Ramanadham et al., 1989; Sakurai et al., 1990; Sekar et al., 1989; Strout et al., 1990). A comparative study has demonstrated that organic vanadium compounds are much safer as antidiabetic agents than inorganic vanadium salts (Reul et al., 1999). In those experiments, diabetic rats receiving organic compounds did not exhibit gastrointestinal side effects and did not develop diarrhea.

Jeju Island, the largest island in Korea, is a volcanic island located about 140 km south of the Korean peninsula. Recently, Jeju water containing vanadium has been reported to have beneficial effects in the treatment of diabetes via activation of AMP-activated protein kinase (Hwang and Chang, 2012) and inhibits preadipocyte differentiation and adipogenesis in obesity animal models (Park et al., 2013).

For the present study, *B. napus* was nutricultured with vanadium-containing Jeju water. During that process, the *B. napus* bioaccumulated vanadium from the Jeju water vanadium concentrate. The present study focused on the antidiabetic effects of BEVC to assess its potential as a functional food ingredient source.

Materials and methods

Extraction of *B. napus* containing vanadium

The *B. napus* was nutricultured for 7 days with a vanadium concentrate (0.06 ± 0.03 mg/L) obtained from Jeju water. The *B. napus* culture took place under controlled environmental conditions (20 ± 3 °C, $55 \pm 5.0\%$ relative humidity) using sprout grower (SHINCHANG INC, SC-9000T, Gyeonggi-do, Korea). After 7 days, extraction of the nutricultured *B. napus* of whole part was performed by juicers (HD-2233, household appliances Co. Ltd., Incheon, Korea). The vanadium content of the *B. napus* extract containing vanadium (BECV) was measured as follows. 5.0 g of BECV was precisely taken into a microwave Teflon vessel and 10 mL of 65% nitric acid (Suprapur, Merck, Darmstadt, Germany) was added. The digestion vessel was placed in a microwave unit (START D, Milestone, Sorisole, Italy) and temperature was raised to 180 °C for 20 min using a microwave digestion system, followed by holding for 15 min. After digestion was completed, decomposed BECV was cooled and filtered through a 0.45 μm syringe filter (PTFE, Whatman, Cardiff, Wales, UK), placed in a 25 mL volumetric flask and diluted with ultrapure water. Standard solutions were prepared by diluting the quality control standard (Perkin Elmer, Shelton, USA) with 2% nitric acid (concentrate of standard solution 0.01–1 mg/L). Samples and standard solutions were analyzed by ICP-OES (Optima 7300DV, Perkin Elmer, Shelton, USA). The vanadium content of BECV is 0.083 mg/L.

Animal model and experimental groups

Prior to antidiabetic effect testing, 6-week-old *db/db* male mice purchased from DH Biolink (Chungbuk, Korea) were acclimatized for 1 week. All experimental protocols were approved by the Institutional Animal Care and Use Committee of Chungbuk National University (CBNUA-306-11-02). Three mice per cage were housed under controlled environmental conditions (22 ± 3 °C, $50 \pm 10\%$ relative humidity, 200–300 Lux). The *db/db* mice were divided into five groups ($n = 6$ in each group). The control group was administered distilled water, the positive control group was administered metformin (30 mg/kg body weight), and the three experimental groups were administered BEVC containing different concentrations of vanadium. All administrations were performed daily by oral gavage. Vanadium concentrations in the three BEVC-administered groups were 0.028, 0.14, and 0.7 $\mu\text{g/kg}$ of mouse body weight. Body weight, feed intake, and water intake of the mice were checked weekly. Mouse blood glucose levels were

checked every 2 weeks over the 8-week study period. Glycated hemoglobin (HbA1c) levels were measured after the end of the 8-week study period.

Intraperitoneal glucose tolerance test

The *db/db* mice were fasted for 12 h prior to the start of the tolerance experiment, and BECV (0.028, 0.14, or 0.7 $\mu\text{g/kg}$; as vanadium concentration in BECV) was intraperitoneally administered 30 min prior to glucose challenge. Glucose (2 g/kg) was intraperitoneally administered at 0 min, and blood glucose levels were measured at 0, 30, 60, 90, 120, and 180 min after glucose administration.

Blood glucose and glycated hemoglobin (HbA1c) levels

Every 2 weeks during the 8-week experiment, blood glucose levels were measured after the animals were fasted for 3 h. Blood glucose levels were determined in blood samples obtained from the tail vein by using an Accu-Chek Performa blood glucose meter (Roche, Mannheim, Germany).

Using blood samples collected from *db/db* mice at the end of the 8 week study period, percentage HbA1c levels were determined by using an HbA1c analyzer (EasyA1c, Infopia, Anyang, Korea).

Blood biochemical examination

Serum samples were used to determine the total cholesterol (TC), triglyceride, and high-density lipoprotein (HDL) cholesterol levels by applying enzymatic methods and an automatic analyzer (Hitachi 7080 Clinical Analyzer, Hitachi, Tokyo, Japan).

Statistical analysis

All data were analyzed with SPSS 12.0 statistical software (SPSS, Chicago, IL, USA). Data are expressed as mean $\pm$ standard deviation values. Statistical differences were examined independently by applying Student's *t* test and Pearson's correlation test. A *p* value < 0.05 was considered significant.

Results and discussion

Effects of BECV on body weight, feed intake, and water intake

The aim of this study was to investigate the antidiabetic effect of a vanadium-containing *B. napus* extract and its potential for use as a source of functional food ingredients.

Fig. 1 Weekly changes in body weight of *db/db* mice administered BECV, metformin, or water (control) orally. Data points indicate mean $\pm$ SD (*n* = 6 in each group)

The effects on body weight, feed intake, and water intake after BECV administration were examined over an 8 week period in *db/db* mice. The mean body weights of the mice did not differ significantly among the five study groups (Fig. 1). The body weight of all of the mice increased similarly during the 8-week study period. Significant differences in feed intake and water intake of the three experimental groups (BECV-treated groups), the positive control group (metformin-treated group), and the control group seemed to be invisible (data not shown).

Effects of BECV on glucose tolerance

Intraperitoneal glucose tolerance was assessed in order to determine the effect of a single oral dose of BECV on glucose tolerance in *db/db* mice (Table 1). Glucose challenge dramatically increased the blood glucose levels in the control group mice, whereas the metformin treatment in the positive control group significantly prevented blood glucose levels from rising, especially at 30 min after glucose load. The changes in the blood glucose levels of the three BECV-treated groups did not differ from that in the control group.

Insulin receptors do not recognize insulin, resulting in insulin resistance, leading to the development of type 2 diabetes (Eledrisi et al., 2006). As a result, Glucose transporters are unable to migrate to the cell membrane and hyperglycemia is maintained without glucose uptake in the blood (Bornfeldt and Tabas, 2011). Greer and peers published data obtained from 10-week-old *db/db* mice and reported that mouse blood glucose and insulin levels increased, compared to those in their control mice (Greer et al., 2006), thus indicating that the mice exhibited insulin resistance.

Impaired glucose tolerance (IGT) is a pre-diabetic state of hyperglycemia that is associated with insulin resistance and increased risk of cardiovascular pathology. IGT may

Table 1 Glucose tolerance test results in *db/db* mice administered BECV, metformin, or water (control)

Groups	Time (min)					
	0	30	60	90	120	180
Control ^a	322 ± 37	583 ± 22	600 ± 0	600 ± 0	600 ± 0	600 ± 0
Metformin 30 mg/kg	260 ± 57	472 ± 58**	581 ± 24*	529 ± 18**	468 ± 35**	395 ± 52**
BECV 0.028 µg/kg	322 ± 29	570 ± 45	600 ± 0	600 ± 0	600 ± 0	600 ± 0
BECV 0.14 µg/kg	303 ± 27	580 ± 18	600 ± 0	600 ± 0	600 ± 0	594 ± 8
BECV 0.7 µg/kg	322 ± 29	570 ± 45	600 ± 0	600 ± 0	600 ± 0	567 ± 27

Data are expressed as the mean ± SD (n = 6)

BECV: Extract of nutricultured *Brassica napus* containing vanadium

^aNegative control: without extract; treated with aseptic water

* $p < 0.05$, ** $p < 0.01$

precede type 2 diabetes mellitus by many years. IGT is also a risk factor for mortality.

Effects of BECV on blood glucose

Mouse blood glucose levels were checked every 2 weeks for 8 weeks. At 8 weeks, the blood glucose levels of two of the BECV-treated groups (0.14 and 0.7 µg/kg groups) were significantly lower than those of the control group (487 ± 44 mg/L and 473 ± 70 vs. 600 ± 24 mg/L, respectively; Table 2). In contrast, the blood glucose level of the 0.7 µg/kg BECV-treated group was similar to that of the positive control group (473 ± 70 vs. 430 ± 16 mg/L).

Vanadium has been reported to possess diverse pharmacological properties, such as insulin mimetic effects (Sekar et al., 1990), as well as superoxide and nitric oxide scavenging effects (Ashiq et al., 2009). In addition, vanadium has been reported to exhibit beneficial effects on the reduction of both type 1 and 2 diabetes by normalizing glucose transport and improving insulin resistance (Briard et al., 1990; Meyerovitch et al., 1987).

Metformin, a biguanide antidiabetic agent that can be administered either alone or in combination with

sulfonylureas, has been extensively used in Europe and Canada. The mechanism of action of metformin suggest that metformin may act in part by both increasing the binding of insulin to its receptor and potentiating insulin action (Vigneri and Goldfine, 1987). Its blood glucose-lowering effects are initially due to inhibition of hepatic glucose production and increased peripheral glucose utilization (Nyane et al., 2017). Several drugs, such as Sulfonylureas, Thiazolidinedione, and Meglitinide, have been shown to regulate blood glucose, but it have been reported to have side effects of weight gain (Sekar et al., 1990). However, the BECV used in this study exhibited the possibility of lowering blood glucose without side effects.

Effects of BECV on glycated hemoglobin (HbA1c)

HbA1c is now formally endorsed in many countries as a diagnostic test for (type 2) diabetes as well as for monitoring, although some debate still continues regarding its applicability for diagnosis (Florkowski, 2013).

In this study the HbA1c level was monitored after 8 weeks. The HbA1c levels of all three BECV-treated groups (0.028, 0.14, and 0.7 µg/kg) were significantly

Table 2 Biweekly blood glucose levels in *db/db* mice administered with BECV, metformin, or water (control)

Groups	Weeks				
	0	2	4	6	8
Control ^a	323 ± 57	365 ± 48	419 ± 11	486 ± 34	600 ± 0
Metformin 30 mg/kg	350 ± 82	361 ± 47	365 ± 54	372 ± 29**	430 ± 16**
BECV 0.028 µg/kg	303 ± 18	369 ± 44	400 ± 39	480 ± 34	542 ± 38
BECV 0.14 µg/kg	313 ± 12	372 ± 42	424 ± 79	455 ± 65	487 ± 44**
BECV 0.7 µg/kg	320 ± 10	318 ± 79	377 ± 38	408 ± 56	473 ± 70**

Data are expressed as the mean ± SD (n = 6)

BECV: Extract of nutricultured *Brassica napus* containing vanadium

^aNegative control: without extract; treated with aseptic water

** $p < 0.01$

Fig. 2 Glycated hemoglobin (HbA1c) levels in *db/db* mice administered with BECV, metformin, or water (control) at the end of the 8-week treatment period. Data points indicate mean $\pm$ SD ($n = 6$ in each group). ** $p < 0.01$

lower than that of the control group ($9.88 \pm 0.33\%$, $9.64 \pm 0.40\%$, and $8.40 \pm 0.36\%$ vs. $10.97 \pm 0.56\%$, respectively; Fig. 2). Also, the HbA1c levels of the $0.7 \mu\text{g/kg}$ BECV-treated group was similar to that in the positive control group ($8.40 \pm 0.36\%$ vs. $8.36 \pm 0.38\%$).

In addition, the 9-week-old control mice had a mean HbA1c level of $10.97 \pm 0.56\%$, indicating that the reduced HbA1c level following BECV treatment is the result of increased insulin sensitivity.

Effects of BECV on serum lipid concentration

The effect of BECV on serum lipid concentrations was examined after completion of the 8-week BECV administration period in *db/db* mice. There were significant differences in most of the lipid profiles between the three experimental groups and the control group (Table 3). Serum concentration of triglyceride in the $0.7 \mu\text{g/kg}$ BECV-treated group was lower than that in the control group (106.5 ± 14.3 vs. $161.1 \pm 29.8 \text{ mg/L}$). In addition,

the TC levels of all three BECV-treated groups (0.028 , 0.14 , and $0.7 \mu\text{g/kg}$ groups) were significantly lower than that of the control group (172.3 ± 7.5 , 174.6 ± 8.7 , and 177.1 ± 4.9 vs. $206.1 \pm 15.3 \text{ mg/L}$, respectively). However, differences in HDL cholesterol levels in the BECV-treated mice were not significantly different from that in the control group.

In the present study, the BECV-treated mice had significantly decreased triglyceride and TC levels. Qin et al. (2003) reported that triglyceride and TC levels were decreased by administration of a cinnamon extract in rats treated with streptozotocin for 3 weeks. The mechanism for such reductions involves AMPK-enhanced triacylglycerol lipase activity increasing glycogen synthesis in the liver and enhancing glucose uptake in skeletal muscle and adipocytes. In mice with HFD-induced obesity, Jeju ground water(containing vanadium) decreased HFD-induced body weight gain and reduced total cholesterol, triglyceride, and glucose levels in the plasma compared to control mice. Taken together, Jeju ground water(containing vanadium) inhibits preadipocyte differentiation and adipogenesis in obesity animal models (Park et al., 2013).

The results of this study show anti-hyperglycemic effects of BECV at dosages of 0.028 , 0.14 , and $0.7 \mu\text{g/kg}$ (as the vanadium concentration in BECV). The BECV treatment decreased blood glucose and HbA1c levels in the treated mice. However, body weight, food intake, and water intake were not significantly affected in the BECV-treated mice. The results suggest that BECV induces hypoglycemic effects, and it may be effective in the treatment of type 2 diabetes. Further investigation is necessary to determine the exact mechanisms responsible for the antidiabetic effect of BECV.

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Table 3 Serum lipid levels in *db/db* mice administered with BECV, metformin, or water (control) at the end of the 8-week treatment period

Groups	Total cholesterol (mg/dl)	Triglyceride (mg/dl)	HDL-cholesterol (mg/dl)
Control ^a	206.1 ± 15.3	161.1 ± 29.8	109.4 ± 8.6
Metformin 30 mg/kg	$149.1 \pm 35.6^{**}$	$94.0 \pm 14.3^{**}$	100.0 ± 11.7
BECV 0.028 $\mu\text{g/kg}$	$172.3 \pm 7.5^{**}$	153.1 ± 19.9	108.0 ± 4.6
BECV 0.14 $\mu\text{g/kg}$	$174.6 \pm 8.7^{**}$	146.7 ± 27.7	107.9 ± 5.9
BECV 0.7 $\mu\text{g/kg}$	$177.1 \pm 4.9^{*}$	$106.5 \pm 14.3^{**}$	104.4 ± 7.9

Data are expressed as the mean $\pm$ SD ($n = 6$)

BECV: Extract of nutricultured *Brassica napus* containing vanadium

^aNegative control: without extract; treated with aseptic water

* $p < 0.05$, ** $p < 0.01$

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