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Antioxidative effects of *Cinnamomi cassiae* and *Rhodiola rosea* extracts in liver of diabetic mice

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Abstract. Both *Cinnamomi cassiae* and *Rhodiola rosea* extracts are used as anti-diabetic folk medicines. Recently, increased oxidative stress was shown to play an important role in the etiology and pathogenesis of diabetes mellitus and its complications. This study was designed to examine the effects of *Cinnamomi cassiae* and *Rhodiola rosea* extracts on blood glucose, lipid peroxidation, the level of reduced glutathione and its related enzymes (glutathione reductase, glutathione S-transferase), and the activity of the antioxidant enzymes (catalase, superoxide dismutase and glutathione peroxidase) in the liver of db/db mice.

Diabetic C57BL/Ks db/db mice were used as experimental models. Mice were divided into control ($n = 10$), *Cinnamomi cassiae* (200 mg/kg/day, $n = 10$), and *Rhodiola rosea* (200 mg/kg/day, $n = 10$) treated groups for 12 weeks of treatment. These type II diabetic mice were used to investigate the effects of *Cinnamomi cassiae* and *Rhodiola rosea* on blood glucose, reduced glutathione, glutathione reductase, glutathione S-transferase, glutathione peroxidase, lipid peroxidation, catalase and superoxide dismutase.

Cinnamomi cassiae and *Rhodiola rosea* extracts significantly decreased on blood glucose, increased levels of reduced glutathione and the activities of glutathione reductase, glutathione S-transferase, glutathione peroxidase, catalase and superoxide dismutase in the liver. Extract treatment also significantly decreased lipid peroxidation.

Cinnamomi cassiae and *Rhodiola rosea* extracts may be effective for correcting hyperglycemia and preventing diabetic complications.

Keywords: *Cinnamomi cassiae*, *Rhodiola rosea*, diabetes, blood glucose level, antioxidant enzymes

Abbreviations: CAT, catalase; Cinnamon, *Cinnamomi cassiae*; FBG, fasting blood glucose level; GSH, reduced glutathione; SOD, superoxide disumtase; GSH-Px, glutathione peroxidase; GST, glutathione S-transferase; GRE, glutathione reductase; GSSG, oxidized glutathione; LPO, lipid peroxidation; MDA, malondialdehyde; MHCP, methylhydroxychalcone polymer; ROS, reactive oxygen species; Rhodiola, *Rhodiola rosea*; SAS, statistical analysis system.

1. Introduction

Diabetes is a chronic metabolic disorder characterized by hyperglycemia and the inability of tissues to utilize glucose. This hyperglycemia increases oxidative stress through overproduction of reactive oxygen species (ROS) [13,20,35]. These ROS contribute to organ injury in systems such as the heart and liver [17,25,32], and oxidative damage is increased in diabetes [34]. Oxidative stress results form an imbalance between radical-generating and radical-scavenging systems: increased free radical production,

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reduced antioxidant defenses, or both [28]. Several antioxidants derived from plant material are effective antioxidants [21,23,28].

Cinnamomi cassiae (Cinnamon bark; Lauraceae) is a traditional folk herb used in Korea, China and Russia for diabetes mellitus [3,36]. The main components are cinnamic aldehyde [12], cinnamic acid [15], tannin [15] and methylhydroxychalcone polymer (MHCP) [16].

Rhodiola rosea is a traditional folk plant used in Korea, China and Russia for traditional folk medicine [6]. The chief components are salidroside, rosavin, p-tyrosol, flavonoid, monoterpene glycoside, cyanoglycoside, penthyl glycoside, aliphatic glycoside, phenylpropanoid and proanthocyanidin [8].

Recently, several studies examined the clinical potential of *Cinnamomi cassiae* (cinnamon) and *Rhodiola rosea* (Rhodiola) extracts, but there are no pharmacological studies to support their anti-diabetic or antioxidant effects. We therefore evaluated the anti-diabetic and antioxidant effects of cinnamon and rhodiola extracts in db/db mice.

2. Materials and methods

2.1. Preparation of cinnamon and rhodiola extracts

The *Cinnamomi cassiae* (cinnamon) used in this experiment was obtained from Draco Natural Products, Inc. (USA), and contained 5% cinnamonaldehyde. Cinnamon (1 kg) was extracted with 640 ml of water for 16 h at 90°, 2 times. The water extract was lyophilized and stored at room temperature until use. Dry yield was 8% (w/w).

Rhodiola rosea (rhodiola) was collected in October 2003 in China. Rhodiola (1.3 kg) was dissolved in 1,000 ml of 85% ethanol as solution for 2 h at 73–75°, 3 times. The extract solution was centrifuged and the upper liquid was lyophilized, 18 g of power was obtained with an extraction yield of 3%. The dried extract stored in refrigerator at 2–8° for until use. The dried extract was dissolved in distilled water, just before use.

2.2. Animals and treatment

All experiments were performed on male C57BL/Ks db/db mice (6 weeks) purchased from Harlan Customer Services Center (USA); the animals were left to acclimatize for one week before the experiment period. The animals were housed in plastic cages in an air-conditioned room with controlled temperature ($23 \pm 3°C$), automatic lighting (on a 12-h light/12-h dark cycle), humidity ($70 \pm 10\%$) throughout the experimental period. All experiment animals were given free access to standard pellets (Samtako Experimental Animals, Korea) and water.

Mice were divided into three groups: saline group (control), 200 mg/kg BW cinnamon extract treatment group (C200), and 200 mg/kg BW rhodiola extract treatment group (R200). The cinnamon and rhodiola extracts were dissolved with saline, and oral saline or cinnamon and rhodiola extracts loading were carried out daily for 12 weeks.

Weighing the residual diet each day, the food intake per mice per day was monitored. At the end of the experiment period, the animals were sacrificed and blood and tissue samples were removed for analysis. The mice were anesthetized with ether and sacrificed after 12 h of fasting. Blood samples were collected from the hepatic portal vein into a vacutainer (Becton Dickinson & Co., Rutherford, NJ, USA) for the separation of serum and centrifuged (3,000 rpm for 15 min at 4°C). The serum was frozen at -70°C for the biochemical analysis. The liver tissue was removed, washed with ice-cold saline. The samples were stored at -70°C in a deep freezer until assay.

2.3. Biochemical measurements

2.3.1. Blood glucose level

The effects of administration of cinnamon and rhodiola extracts to db/db mice were measured fasting blood glucose level (FBG) at 0, 2, 4, 8 and 12 weeks. FBG was determined in tail blood samples at 10:00 a.m. using a Glucose Analyzer (Glucotrend 2, Germany).

2.3.2. Homogenized in liver tissues

Liver was homogenized in 0.1 mol/l sodium phosphate buffer (pH 7.4) and centrifuged (8,000 rpm for 20 min at 4°). Homogenate was used for all assays.

2.3.3. Lipid peroxidation (LPO) assay

Malondialdehyde (MDA) is an end product of membrane lipid peroxidation. The enhanced production of MDA in tissues is an index of oxidative stress. Therefore, MDA concentration was estimated by the method of Ohkawa et al. [27]. 0.4 ml homogenate was added to 0.1 M potassium phosphate buffer (0.4 ml), and 0.4 ml of the mixture was incubated for 4 h at 37°. 0.2 ml of 8.1% sodium dodecyl sulfate, 1.5 ml of 20% acetic acid and 1.5 ml of 0.8% thiobarbituric acid were added, vortexed, and placed in boiling water bath in tubes for 10 min. The samples were allowed to cool at room temperature. n-Butanol:pyridine (15:1) was added, vortexed and centrifuged at 3,000 rpm for 15 min. 3 ml of the colored pink layer was measured at 532 nm. The level of lipid peroxides is expressed as nmol MDA /mg protein.

2.3.4. Catalase (CAT) assay

CAT activity was assessed using a modified method of spectro-photometric method [30]. The cells were pottered, and 20 ul of 35% H_2O_2 added to 1 ml of homogenate at 25°. The reaction was started by adding H_2O_2 after mixing with a plastic paddle. The decrease in absorbance was recorded for about 30 sec at a wavelength of 240 nm against a blank containing 1 ml PBS and 0.5 ml H_2O_2.

2.3.5. Superoxide dismutase (SOD) assay

SOD activity was assayed by the method of Marklund and Marklund [1]. This method is based on the pyrogallol autoxidation which is followed at 440 nm. The pyrogallol autoxidation is highly dependent on O_2^- and is inhibited by the presence of SOD. Cytosolic fraction was diluted 1:10 (v/v) in 0.1 M potassium phosphate buffer, pH 7.4, preincubated for 5 min at room temperature, added 7.2 mM pyrogallol (0.2 ml) and incubated for 10 min at room temperature. The reaction was stopped by the addition of 5 N of hydrochloric acid. One unit of SOD activity is defined as the amount of SOD that inhibits 50% the pyrogallol autoxidation. The specific activity is represented as units per mg protein.

2.3.6. Glutathione peroxidase (GSH-Px) assay

GSH-Px activity was measured specrophotometrically using a technique based on method of Paglia and Valentine [26], whereas GSH formation was assayed by measuring the conversion of NADPH to NADP. Enzyme activity was expressed as μmole of NADP/min/mg protein.

2.3.7. Reduced glutathione (GSH) assay

Reduced GSH level was performed by a slight modification of published method of Sedlak and Lindsay [31]. The scrapped hepatocytes were sample was homogenized with 0.1 M sodium phosphate buffer, pH 7.2. The homogenized mixture was then centrifuged at 3,000 rpm for 20 min. The supernatant

was collected for GSH and protein assay. 0.5 ml of supernatant was mixed with 0.5 ml of 4% 5-sulfosalicylic acid. The mixture was centrifuged at 3,000 rpm for 10 min and the supernatant was mixed with and 2.7 ml of 0.1 M 5,5′-dithiobis-2-nitrobenzoic acid and kept at 25° for 20 min. The absorbance of the resultant mixture was measured at 412 nm. The reduced form of GSH was used to construct the standard curve for the calculation of GSH level. The final GSH level was expressed as μmole of GSH per mg protein.

2.3.8. Glutathione reductase (*GRE*) *assay*

GRE activity was assayed according to the method of Carlberg and Mannervik [4]. The rate of oxidation of NADPH by GSSG at 30° was used as a standard measure of enzymatic activity. The reaction system of 1 ml contained 1.0 mM GSSG, 0.1 mM NADPH, 0.5 mM EDTA, 0.1 M sodium phosphate buffer, pH 7.6, and a suitable amount of the GRE sample to give a change in absorbance of 0.05 to 0.30/min. The oxidation of 1 μmol of NADPH/min under these conditions is used as a unit of GRE activity.

2.3.9. Glutathione S-transferase (*GST*) *assay*

GST activity was assayed according to the method of Habig et al. [11]. The incubation mixture contained 30 μg protein of the homogenate fraction and 0.5 ml of glutathione (0.5 mM) in 0.1 M sodium phosphate buffer, pH 7.3. After preincubation at 37°C for 5 min the reaction was initiated by adding 50 μl of 1-chloro-2,4-dinitrobenzene (CDNB) at 0.5 mM in the incubation mixture and incubated at 37°C for another 5 min. Trichloroacetic acid solution (0.2 ml, 33%) was added to terminate the reaction. After centrifugation, the CDNB conjugate was measured in the supernatant at 340 nm. Calculations were made using a molar extinction coefficient of 9.6 mM^{-1} cm^{-1}. A unit of enzyme activity is defined as the amount of enzyme that catalyzes the formation of 1 μmol of CDNB conjugate/min/mg protein under the assay conditions.

2.3.10. Protein determination

Protein concentration was determined by Lowry's method using bovine serum albumin as a standard [22].

2.3.11. Statistical analysis

Data are presented as mean $\pm$ standard deviation (SD) in each group. Results were statistically analyzed by analysis of variance (SAS). Comparison between control group and treatment group were analyzed by Student's t-test. Differences of $P < 0.05$ were considered significant.

3. Results

3.1. Mean body weight and liver index

The mean body weights and liver index (liver weight $\times$ 100/body weight) are shown in Table 1. The final body weights of the cinnamon and rhodiola extracts treated mice and the controls were not significantly different, but changes of body weights in the control group increased, but decreased in the treatment groups. The mean body weight of the rhodiola-treated animals was significantly decreased (25% of controls, $P < 0.05$). The liver index of the cinnamon extract group was lower than controls (4.13 $\pm$ 0.29% and 4.40 $\pm$ 0.91%, respectively). Significant liver atrophy was observed in the rhodiola extract group (7% of controls, $P < 0.05$).

Table 1
Effect of cinnamon and rhodiola extracts on changes of body weight (g) and liver index (%) in diabetic mice

Group	Initial weight (g)	Final weight (g)	Changes of body weight (g)	Liver Index (%)
Control	40.52 ± 3.12	51.23 ± 4.84	10.51 ± 3.60	4.40 ± 0.91
Cinnamon	40.87 ± 2.03	48.57 ± 3.18	8.31 ± 3.55	4.13 ± 0.29*
Rhodiola	40.43 ± 4.57	48.33 ± 5.61	7.83 ± 3.32*	4.08 ± 0.49*

Values are mean ± S.D. The means not sharing a common letter are significantly different between control and treatment groups ($p < 0.05$).

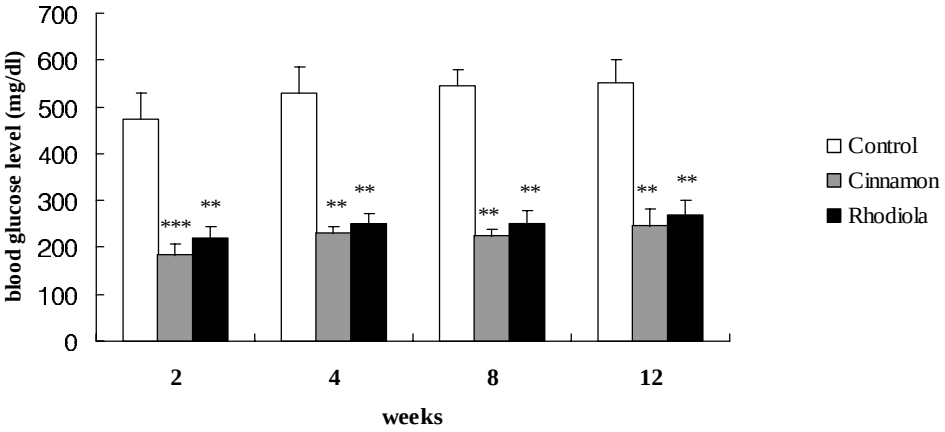

Fig. 1. Effect of cinnamon and rhodiola extracts on blood glucose level in diabetic mice. Values are mean ± S.D. The means not sharing a common letter are significantly different between control and treatment groups ($P < 0.05$).

3.2. Fasting blood glucose level

Administration of cinnamon and rhodiola extracts affected blood glucose levels in db/db mice (Fig. 1). Fasting blood glucose level was measured after animals fasted for 18 h. The mean blood glucose concentration in cinnamon-treated animals was 2.6 times, 2.3 times, 2.4 times and 2.1 times lower than controls (475.0 ± 53.5 and 184.2 ± 23.7 mg/dl, 529.2 ± 55.9 and 227.8 ± 16.7 mg/dl, 544.8 ± 34.8 and 223.0 ± 16.4 mg/dl, 552.4 ± 49.4 and 268.6 ± 3.4 mg/dl, respectively) at 2, 4, 8 and 12 weeks, respectively.

Rhodiola extract also significantly lowered blood glucose levels ($P < 0.01$). The mean blood glucose levels of the rhodiola extract was 54%, 52.8%, 54.2% and 51.4% lower than controls (475.0 ± 53.5 and 218.6 ± 26.7 mg/dl, 529.2 ± 55.9 and 249.7 ± 24.2 mg/dl, 544.8 ± 34.8 and 249.7 ± 30.2 mg/dl, 552.4 ± 49.4 and 268.6 ± 31.4 mg/dl, respectively) at 2, 4, 8 and 12 weeks, respectively.

The decline in fasting blood glucose level peaked at 2 weeks and remained almost constant after 4 and 6 weeks of cinnamon and rhodiola treatment.

3.3. Lipid peroxidation (*LPO*)

There was a significant elevation in MDA in the control group (Fig. 2). Cinnamon treatment significantly decreased MDA levels by 65.5% ($P < 0.01$), and rhodiola treatment decreased MDA levels by 44.3% versus control ($P < 0.05$).

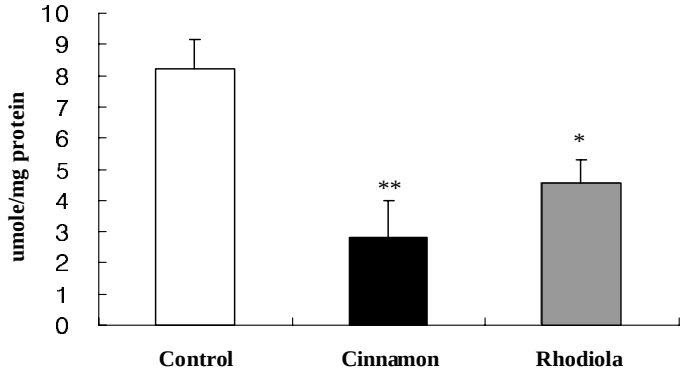

Fig. 2. Effect of administration of cinnamon and rhodiola extracts on lipid peroxidation activity in db/db mice. Values are mean ± S.D. The means not sharing a common letter are significantly different between control and treatment groups ($P < 0.05$).

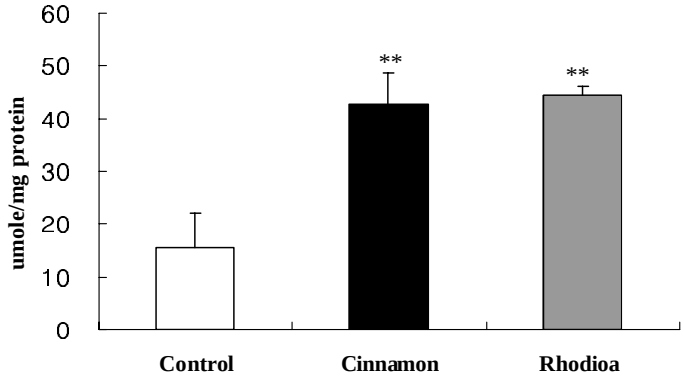

Fig. 3. Effect of administration of cinnamon and rhodiola extracts on reduced glutathione activity in db/db mice. Values are mean ± S.D. The means not sharing a common letter are significantly different between control and treatment groups ($P < 0.05$).

3.4. Reduced glutathione (*GSH*)

The hepatic GSH levels were lower in controls, but cinnamon and rhodiola treatment markedly improved GSH levels. (63.0% and 64.5%, respectively; Fig. 3).

3.5. Glutathione peroxidase (*GSH-Px*)

GSH-Px activity in liver homogenates was reduced in control mice. Cinnamon and rhodiola administration significantly increased (30.8% and 23.3% of control, respectively) GSH-Px levels when compared to control ($P < 0.05$, Fig. 4).

3.6. Glutathione S-transferase (*GST*)

GST levels in the liver were reduced in controls. Cinnamon and rhodiola administration significantly increased in GST when compared to control group (46.0% and 42.1% of control, respectively, $P < 0.05$, Fig. 5).

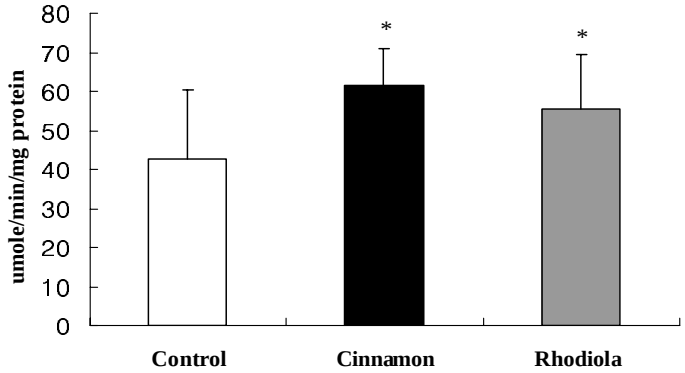

Fig. 4. Effect of administration of cinnamon and rhodiola extracts on glutathione peroxidase activity in db/db mice. Values are mean ± S.D. The means not sharing a common letter are significantly different between control and treatment groups ($P < 0.05$).

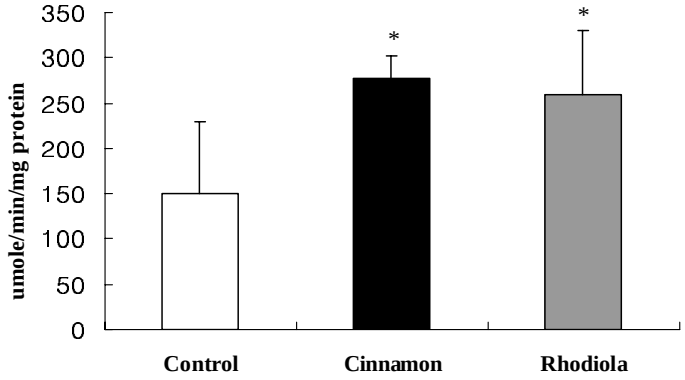

Fig. 5. Effect of administration of cinnamon and rhodiola extracts on glutathione S-transferase activity in db/db mice. Values are mean ± S.D. The means not sharing a common letter are significantly different between control and treatment groups ($P < 0.05$).

3.7. Glutathione reductase (*GRE*)

GRE activity was significantly decreased in controls. A significant increase (59.7% of control, $P < 0.01$) in the levels of GRE was observed cinnamon extract when compared with control mice. Rhodiola also showed less significant increase in the GRE when compared with control mice (46.8% of control, $P < 0.05$; Fig. 6).

3.8. Catalase (*CAT*)

CAT activity in liver homogenates was reduced in controls, and cinnamon and rhodiola treatment increased CAT activity (26.1% and 22.7% of controls, respectively, Fig. 7).

3.9. Superoxide dismutase (*SOD*)

SOD levels were reduced in control. Cinnamon extract showed significant increase in SOD when compared to control (56.5% of control, $P < 0.01$). Rhodiola extract showed increase in SOD in the liver homogenate compared to control (30.9% of control, Fig. 8).

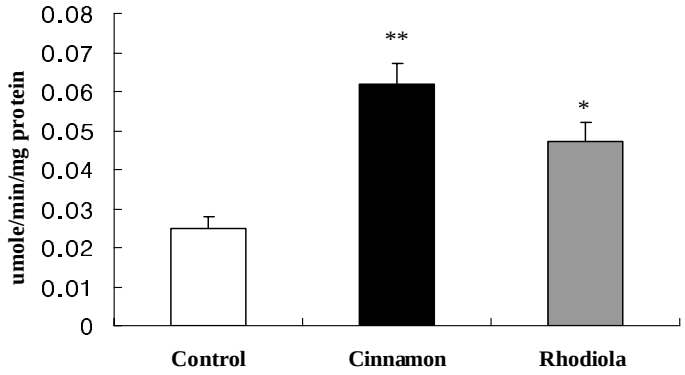

Fig. 6. Effect of administration of cinnamon and rhodiola extracts on glutathione reductase activity in db/db mice. Values are mean ± S.D. The means not sharing a common letter are significantly different between control and treatment groups ($P < 0.05$).

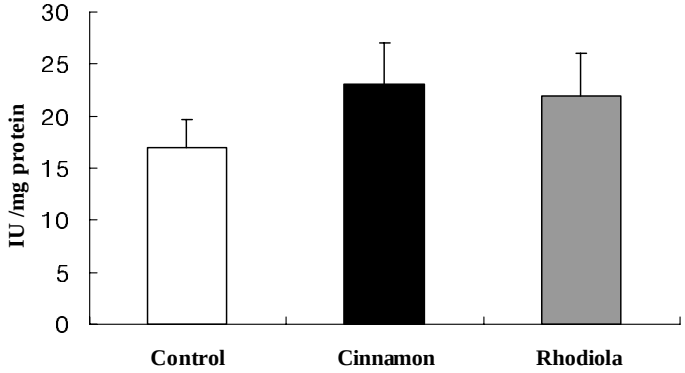

Fig. 7. Effect of administration of cinnamon and rhodiola extracts on catalase activity in db/db mice. Values are mean ± S.D. The means not sharing a common letter are significantly different between control and treatment groups ($P < 0.05$).

4. Discussion

The current study examined the ability of cinnamon and rhodiola extracts to regulate hyperglycemia and oxidative stress in db/db mice. We measured body weight and fasting blood glucose after treatment with cinnamon and rhodiola extracts. Cinnamon and rhodiola treatment significantly decreased ($P < 0.05$) mean body weight and the liver index compared with controls (Table 1). Cinnamon and rhodiola extracts decreased food consumption and increased body weight gain to a marked extent, increasing energy efficiency and attenuating muscle wasting.

The elevated blood glucose level at both the start (2 weeks) and end (12 weeks) of the experiment indicates the presence of continuous hyperglycemia in the control group, whereas cinnamon and rhodiola extracts markedly lowered fasting blood glucose. Similar to our results, an anti-hyperglycemic effect has been reported with several plants [21,23,28]. Cinnamon and rhodiola may potentiate the effects of insulin by either increasing its secretion from existing langerhan's cells, or by its release from the bound form [9].

Cinnamon and rhodiola extracts might increase glucose transport and insulin sensitivity, or alternatively might block the conversion of carbohydrates into glucose in the small intestine in a similar way that it

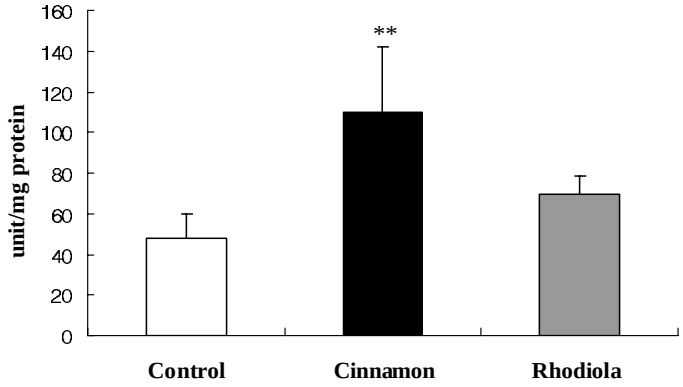

Fig. 8. Effect of administration of cinnamon and rhodiola extracts on superoxide dismutase activity in db/db mice. Values are mean ± S.D. The means not sharing a common letter are significantly different between control and treatment groups ($P < 0.05$).

inhibits the transformation of sucrose, maltose, and oligosaccharides into the monosaccarides glucose, fructose and galactose [7].

In addition, continued hyperglycemia in the diabetic state may increase the production of free radicals by direct autoxidation of glucose [37]. We therefore examined the correlation between the diabetic state and the ROS system, since ROS are the most significant inducers of antioxidant defenses [10,18,19].

Oxidative stress occurs when the balance between oxidants, i.e. ROS, and antioxidants shifts in favor of the ROS. The reactive superoxide anions subsequently give rise to hydrogen peroxide, hydroxyl radicals, and other redox-reactive molecules. An inadequate defense system may be overwhelmed by ROS, leading to damage of proteins, lipids, and DNA, which in turn may result in extensive cell and tissue damage. Cinnamon and rhodiola show antioxidant activity.

LPO, a type of oxidative degradation of polyunsaturated fatty acids, has been linked with altered membrane structure and enzyme inactivation. The activity of liver LPO significantly increased in the controls and was decreased by cinnamon and rhodiola treatment, suggesting that cinnamon and rhodiola extracts might decrease production of free radicals and/or increase antioxidant activity.

SOD catalyses the dismutation of superoxide anions to hydrogen peroxide, which in turn is converted to harmless water and oxygen by the glutathione system. This system includes the enzymes GSH-Px, GST, and GRE. GSH-Px and GST activity require glutathione (GSH) as a co-factor. GSH-Px activity results in oxidized glutathione (GSSG), which can subsequently be recycled to GSH via the enzyme GRE [29].

The activities of liver GST, CAT, SOD, GSH-Px, GRE, and GSH significantly decreased in controls, but were significantly increased by cinnamon and rhodiola, suggesting a capacity of these compounds to reduce oxidative damage in the liver [2,5,14].

Cinnamon and rhodiola extracts also significantly increased SOD compared to controls suggesting that SOD activity might be a scavenger for the free oxygen radicals.

The GST levels in diabetic liver reflect the synthesis of LPOs-GSH [38]. We showed that cinnamon and rhodiola increased the GST content in liver.

GSH-Px is an enzyme that detoxifies peroxides with GSH acting as an electron donor, producing GSSG as an end product [33]. Enhanced GSH-Px activity leads to the increased production of H_2O_2, which agrees with other observations [14]. We showed that cinnamon and rhodiola increased GSH-Px and GRE activity. The enhanced GRE activity indicates increased production of GSH. The GRE enzyme catalyzes

the transformation of oxidized GSSG into deoxidized GSH. GSH is associated with the synthesis of important macromolecules and protection against reactive oxygen compounds [24]. The reduced GSH enzyme affects the pathogenesis of chronic diabetes. Therefore, cinnamon and rhodiola extracts might be novel agents for protecting the liver from diabetic oxidative stress.

In conclusion, we demonstrated that cinnamon and rhodiola extracts are effective in controlling hyperglycemia and oxidative stress in db/db mice. Diabetes increases oxidative stress in hepatic tissue. Cinnamon and rhodiola extracts suppress LPO and controls antioxidant enzymes in diabetic mouse liver. Thus, the protective role of cinnamon and rhodiola extracts might be related to their antioxidant properties. The present results suggest that cinnamon and rhodiola extracts prevent oxidative stress in diabetic liver.

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