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Full Length Research Paper

Antidiabetic and hypolipidemic effects of Ceylon cinnamon (*Cinnamomum verum*) in alloxan-diabetic rats

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The objective of this study was to examine the effects of increasing doses of Ceylon cinnamon's aqueous extract on fasting plasma glycemic and lipidemic profiles, as well as body weight gain, food intake and food efficiency ratio (FER) in alloxan-diabetic rats. Cinnamon extract was administered to rats at different dosages (200, 400, 600 and 1200 mg/kg bw) for thirty days followed by a fifteen day wash out period. After thirty days, the administration of diabetic rats with the lowest dose (200 mg/kg bw) of cinnamon extracts was the most efficient in affecting significant ($P < 0.05$) reduction in the levels of fasting blood glucose (FBG), but no hypoglycaemic activity was observed in the untreated diabetic control rats. Moreover, cinnamon treatment significantly ($P < 0.05$) lowered the serum levels of total cholesterol (TC), high density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol and triglycerides (TG), compared with the diabetic positive control (PC) rats. The observed hypoglycemic and hypolipidemic effects of cinnamon extracts in diabetic rats were associated with significant improvements in body weight gain, FI and FER. While, after the 15-day wash-out period, the level of FBG, TC, LDL and TG gradually increased, they were still lower than that in the diabetic PC group of rats. It can be concluded that cinnamon extract exhibits a modulatory role of glycemic and lipidimic profiles in diabetic rats.

Key words: Diabetes mellitus, Cinnamon, fasting blood glucose, antiglycemic, hypolipidemic, diabetic rats.

INTRODUCTION

The World Health Organization (2008) estimated that ~2.9 million deaths are attributable to Diabetes mellitus (DM) every year, making it the third-largest cause of death in industrialized countries. DM is a progressive chronic disease characterized by hyperglycemia, resulting from insulin resistance, dysfunction of the pancreatic β-cells affecting insulin secretion or both. The two major types of DM include insulin-dependent (ID) and non-insulin-dependent (NID). It is estimated that approximately 90% of diabetic patients are NID, with insulin resistance being the etiological factor that contributes to the development of the disease (Fuller et al., 1980). Long-term effects of this disease, for which there is no cure, lead to multiple organ damage and failure (WHO, 1999). Strikingly, the prevalence of DM is predicted to rise tremendously so that the number of diabetics around the world will be ~366 million by the year 2030 (Wild at al., 2004).

Effective control of blood glucose levels is essential for limiting symptomatic complications associated with diabetes and ameliorating the quality of life in diabetic patients (Bell, 2001). Several oral hypoglycemic synthetic drugs are available together with insulin for treatment of diabetes (Mannucci et al., 2004). However, these agents

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are costly and exert some sever side effects. Efforts for the identification of effective antihyperglycemic agents have been concentrated on natural food products used in folk medicine (Sarma and Das, 2009; Osadolor et al., 2011; Nyunaï et al., 2011). Numerous traditional medicinal herb extracts have been employed for the treatment of DM ascribed to its negligible side effects and cost effectiveness (Kameswara et al., 1997; Broadhurst et al., 2000).

Cylon cinnamon (*Cinnamomum verum,* Lauraceae) is cultivated in various parts of Asian countires, especially in Sri Lanka and Southern India. Cinnamon is one of the traditional folk herbs used in Korea, China and Russia for diabetes mellitus (Bailey and Day, 1989). It is widely used in rice dishes for its pleasing aromatic taste. Powder of cinnamon bark is mixed in the preparation of many kinds of deserts, spices, candies, liqueurs and teas for flavour (Khan et al., 1990). Natural herbs such as cinnamon, cloves, bay leaves and turmeric have been shown to exhibit insulin potentiating activity in glucose metabolism (Khan et al., 1990). The potential effects of forty-nine herbs, spices and medicinal plant extracts on insulin-dependent utilization of glucose by the use of rat epididymal adipocyte assay have been studied. In these experiments, cinnamon was the most active product (Broadhurst et al., 2000). However, many of the phytochemicals in these plants are hypoglycaemic due to their metabolic or hepatic toxicity. It has been reported that one to two thirds of some 1,223 plants screened for bioactivity of lowering blood glucose level may be dangerous to human health (Marles and Fransworth, 1994). Therefore, identifying safer, more effective agents continues to be an important area of active research.

The present study was conducted to evaluate the antidiabetic effect of cinnamon aqueous extract on diabetic male rats. Since insulin plays a key role in lipids metabolism, we postulated that the administration of cinnamon would lead to improved fasting blood glucose and lipid profiles *in vivo*. Therefore, this study was designed to determine, whether, there is an effect of cinnamon on food intake, body weight changes, food efficiency ratio, fasting blood glucose and lipid profiles in alloxan-induced diabetes in male rats.

MATERIALS AND METHODS

Chemicals used

Alloxan monohydrate was purchased from Sigma-Aldrich (MO, IL USA).

Preparation of the plant extract

In this study, Ceylon cinnamon, also known as true cinnamon, which is indigenous to Sri Lanka and named after the old name of Sri Lanka was used. Ceylon cinnamon was purchased from the local market of Riyadh city (Saudi Arabia). Cinnamon bark (1 kg) was extracted with 640 ml of water for 16 h at 90°C, twice. The water extract was lyophilized and then stored at room temperature until further use. Dry yield was 8% (w/w). The lyophilized cinnamon was triturated in normal saline (NS, 0.9%) and orally administered to the rats at particular doses.

Experimental animals

All experiments were performed on male albino rats, weighing 129 ± 5 g, obtained from animal rearing facility of the College of Medicine at King Saud University. Sixty rats were housed throughout the experiment in polypropylene cages, with 10 animals per cage, and allowed to acclimatize to the laboratory environment for 10 days. Animals were maintained under controlled conditions of temperature at 25±2°C, relative humidity of 50±15% and normal photoperiod (12 to 12 h light-dark cycle). The animals were allowed free access to standard dry pellet diet and water *ad libitum* (Aboul-Soud et al., 2011; Al-Othman et al., 2011; El-Shemy et al., 2010). The experiments reported here complied with current laws and regulations of Saudi Arabia on the care and handling of experimental animals and the Animal Ethics Committee of King Saud University, College of Medicine, Saudi Arabia.

Experimental design

The sixty rats in the experiment were divided into 6 groups, 10 rats each. The 1st group served as a negative control or normal control group. The remaining fifty rats were made diabetic with an intrapreritoneal (IP) injection of alloxan (150 mg/kg bw), dissolved in NS solution. Fasting blood glucose (FBG) levels were measured on day three and rats with an FBG level greater than 9.7 mmol/l (175 mg/dl) were included in the study (Yadav et al., 2002). Groups of diabetic rats were as follows: 2nd group, served as a positive control and was orally administered NS solution only for 30 days; the remaining four groups (3rd, 4th, 5th and 6th group) received daily doses of cinnamon extracts (200, 400, 600, and 1200 mg/kg bw), respectively, for thirty days. The wash-out period was from day 31 to 45; during which no cinnamon extracts were given to the rats.

Food efficiency ratio and body weight measurements

Food intake, body weight change and food efficiency ratio (FER) were measured every day. The FER was calculated according to the following equation:

FER = Mean daily body weight gain (g)/ mean daily food intake (g).

Blood sampling

On days 30 and 45, approximately 3 ml of fasting blood samples were collected from all rats (under ether anesthesia) into sterilized centrifuge tubes by puncturing their retro-orbital venous plexus with fine sterilized glass capillary tubes. Blood samples were allowed to clot at room temperature, and then centrifuged at 4000 rpm for 10 min to separate the serum. Serum samples were stored at -80°C for subsequent clinical analyses.

Clinical measurements

Serum levels of fasting blood glucose (FBG), total cholesterol (TC), high density lipoprotein (HDL) cholesterol and triglycerides (TG) were determined by using Vitros Analyzer (Ortho-Clinical Diagnostics Inc., Johnson and Johnson) according to standard protocols (Tietz, 1999; Allain et al., 1974; Warnick and Wood, 1995;

Table 1. Weight gain 30-day after the administration of cinnamon extract and after 15-day wash-out period in male diabetic rats.

Group	Initial wt (g)	Day 30 wt (g)	Weight gain I (g/d)[†]	Day 45 wt (g)	Weight gain II (g/d) [††]
1st	129.50±2.20	260.12±4.20	4.35±0.26[f]	320.30±5.10	4.01±0.30[d]
2nd	128.80±2.16	217.90±2.54	2.27±0.50[e]	244.00±3.83	2.20±0.20[c]
3rd	129.60±2.30	254.10±4.60	4.15±0.39[a]	298.20±6.29	2.74±0.18[*a]
4th	129.20±2.38	248.30±2.19	3.97±0.15[b]	284.00±6.29	2.38±0.23[*b]
5th	129.00±1.58	237.30±3.20	3.61±0.23[c]	269.40±3.04	2.14±0.12[*c]
6th	129.00±2.12	233.70±2.38	3.49±0.22[d]	264.60±3.50	2.06±0.19[*c]

Values are expressed as overall means ± SD; n = 10 for each treatment group. ([†]) weight gain I (g/d) = Initial wt (g) – Day 30 wt (g) ÷ 30. ([††]) weight gain II (g/d) = Day 45 wt (g) – Day 30 wt (g) ÷ 15. ([*]) Indicates significant differences ($P < 0.05$) compared to weight gain I within the same raw (within group). [abcdef] Indicates values within the same column (between groups) not sharing a common superscript letter were significantly different, $P < 0.05$.

Cole et al., 2000). Serum concentration of low density lipoprotein cholesterol was calculated with the Friedwald formula (Friedwald et al., 1972).

Statistical analysis

Analysis of data was performed using Statistical Package for the Social Sciences (SPSS; version 17) computer software. Descriptive statistics were adapted to display data in means ± SD. The paired student's *t*-test was employed to compare the mean values obtained within each group. Data were subjected to one-way analysis of variance (ANOVA) followed by Bonferroni's post-hoc test for multiple comparisons of the mean between treatments and the negative control. The correction method was applied and statistical probabilities P < 0.5 were considered to be significant.

RESULTS

Effect of cinnamon extracts on gain weight gain in diabetic rats

The results of weight gain after 30 days (Period I) administration of 5 doses of cinnamon extract and after 15 days wash-out period (Period II) is shown in Table 1. The mean weight gain during period I of cinnamon extract administered diabetic rats was significantly (P<0.05) greater in rats of the 3rd (treated with cinnamon extract at 200 mg/kg bw) and 4th (treated with cinnamon extract at 400 mg/kg bw) groups than that of diabetic rats of the positive control (PC), which only received normal saline (NS) solution. There was no significant difference between the mean weight gains in diabetic rats of the 5th group (treated with cinnamon extract at 800 mg/kg bw) and those of the 6th group (treated with cinnamon extract at 1200 mg/kg bw). The mean weight gain of diabetic rats during period II (g/d) of the 3rd and 4th group remained significantly (P < 0.05) greater compared with that of the 2nd group (PC). In period II, there was no significant difference in the mean weight gain between rats of the 5th and 6th group compared with that of rats in the 2nd (PC) group. Weight gain during period II of the 3rd, 4th, 5th and 6th groups remained significantly (P < 0.05) lower that that of rats during period I of the same groups, respectively.

Effect of cinnamon extract on food intake and food efficiency ratio

The effect of the administration of diabetic rats with four increasing doses of cinnamon extract on food intake (FI) and food efficiency ratio (FER), both after periods I and II is shown in Table 2. FI (g/d) of diabetic rats during period I, after an administration period of 30 days with cinnamon extract, in the 3rd, 4th, 5th and 6th was significantly (P < 0.05) greater than that in the 2nd (PC) group. The mean FI for diabetic rats in the 3rd group was almost identical with that of the normal rats in the negative control (1st) group. The FI values (g/d) during period II after a 15-d cinnamon extract wash-out period in diabetic rats had the same trend as FI values for rats of the same groups during period I. During period II, FI values of the 1st, 3rd, 4th, 5th and 6th groups was significantly lower than that of rats during Period I, within the same group. The mean of FER during period I in diabetic rats of the 3rd, 4th, 5th, 6th and 6th groups were significantly (P < 0.05) greater than that of the 2nd (PC) group. There were no significant differences among the mean FER values during period I for rats in the 4th, 5th and 6th groups. The mean FER during period II for rats of the 3rd and 5th group was significantly (P < 0.05) greater than that of the 2nd (PC) group, whereas the FER for rats of the 4th and 6th during same period were not significantly different compared to the PC group. The mean FER during period II for rats of the 3rd, 4th, 5th and 5th groups was significantly (P < 0.05) lower than that of FER of the same groups during period I.

Effect of cinnamon extract on blood glucose and lipid profiles

The results of the levels of fasting blood glucose (FBG) and serum lipid profiles (mg/dl) during period I after 30-

Table 2. Food intake and food efficiency ration 30-day after the administration of cinnamon extract and after 15-day wash-out period in male diabetic rats.

Group	Food intake I (g/d)[†]	FER I[§]	Food intake II (g/d)[††]	FER II[§§]
1st	17.68±0.96[a]	0.25±0.05[d]	16.35±1.07[*a]	0.25±0.06[d]
2nd	13.91±1.08[d]	0.16±0.05[c]	13.89±1.03[c]	0.15±0.09[b]
3rd	17.54±1.10[a]	0.24±0.05[a]	15.87±1.01[*a]	0.17±0.07[**a]
4th	17.12±1.03[b]	0.23±0.04[b]	15.31±0.99[*b]	0.15±0.09[**b]
5th	15.24±1.05[c]	0.23±0.06[b]	14.91±1.00[*c]	0.14±0.07[**c]
6th	14.98±1.04[c]	0.23±0.07[b]	14.07±1.06[*d]	0.15±0.09[**b]

Values are expressed as overall means ± SD; n = 10 for each treatment group. ([†]) Food intake I (g/d) = mean daily intakes for 30 days. ([§]) FER I, food efficiency ratio I = weight gain I (g/d) ÷ food intake I (g/d). ([††]) Food intake II (g/d) = mean daily intakes for 15 days. ([§§]) FER II, food efficiency ratio II = weight gain II (g/d) ÷ food intake II (g/d) ([*]) Indicates significant differences ($P < 0.05$) compared to food intake I within the same raw (within group). ([**]) Indicates significant differences ($P < 0.05$) compared to FER I within the same raw (within group). [abcdef] Indicates values within the same column (between groups) not sharing a common superscript letter were significantly different, $P < 0.05$.

Table 3. Fasting blood glucose and serum lipid profiles (mg/dl) 30-day after the administration of cinnamon extract and after 15-day wash-out period in male diabetic rats.

Parameter	FBG	TC	LDL	HDL	TG
1st	89.60±2.26[e]	85.60±2.13[c]	45.92±1.32[c]	36.80±2.10[d]	92.50±2.86[d]
2nd	176.40±4.50[d]	109.60±2.07[d]	75.80±3.56[d]	30.10±2.28[a]	110.00±2.23[c]
3rd	147.20±3.56[a]	87.60±2.50[a]	55.80±1.92[a]	30.00±2.16[a]	96.80±2.86[a]
4th	152.80±4.49[b]	93.40±2.07[b]	59.87±3.70[b]	31.80±1.30[b]	100.60±1.81[b]
5th	159.00±2.91[c]	103.60±2.88[c]	67.40±1.81[c]	34.20±2.28[c]	103.40±1.82[b]
6th	151.40±3.28[ab]	94.00±2.54[b]	60.30±2.70[b]	31.90±1.48[b]	94.20±2.77[a]

Values are expressed as overall means ± SD; n = 10 for each treatment group. [abcdef] Indicates values within the same column (between groups) not sharing a common superscript letter were significantly different, $P < 0.05$. ([§]) FBG, fasting blood glucose; TC, total cholesterol; LDL, low density lipoprotein cholesterol; HDL, high density lipoprotein cholesterol; TG, triglycerides.

days administration of cinnamon extract are depicted in Table 3. During period I, the mean FBG for diabetic rats in the 3rd, 4th, 5th and 6th groups were significantly ($P < 0.05$) than that of the 2nd group (PC). The lowest mean FBG value (172.2±3.56 mg/dl) was observed in rats of the 3rd group compared with that of the 2nd group (176.4±4.5 mg/dl). There was no significant differences in the mean FBG of the 4th and 6th and between the 3rd and 6th group. The mean total cholesterol (TC), low density lipoprotein (LDL) and triglycerides (TG), during period I after a 30-day administration of cinnamon extract, in the 3rd, 4th, 5th and 6th had the same trend as the mean values of FBG. The mean high density lipoprotein (HDL) in rats of the 3rd group was not significantly ($P<0.05$) different from that in the 2nd (PC) group, whereas HDL values were significantly ($P < 0.05$) higher in the same groups compared with the 2nd (PC) group.

Within group comparisons of FBG and serum lipid profiles between periods I (30-day cinnamon administration) and II (15-d wash-out) are shown in Table 4. After period II, the mean FBG, TC, LDL and TG values in the 3rd, 4th, 5th and 6th groups were significantly ($P < 0.05$) greater than those values in the same groups after period I, whereas they were significantly ($P < 0.05$) lower than that of the 2nd (PC) group. Based on data of Tables 3 and 4, the most effective dose in lowering blood glucose and serum profiles of diabetic rats is 200 mg/kg bw (3rd group).

DISCUSSION

Alloxan, a β-cytotoxic agent, rapidly and selectively accumulates in pancreatic β-cells and causes β-cell death and apoptosis by generation of reactive oxygen species (ROS), superoxide radicals and hydrogen peroxide (Gorus et al., 1982; Szkudelski, 2001). β cell death causes hyperglycemia due to insulin deficiency, which further aggravates the oxidative stress induced by alloxan (Kaneto et al., 1996). It has been widely used to induce diabetes mellitus in experimental animal models allowing investigation of hypoglycaemic agents in the treatment of diabetes (Kar et al., 2003; Jayakar et al., 2004). Alloxan injection consistently produced symptoms characteristic of diabetes mellitus inducing

Table 4. Within group comparison of fasting blood glucose and serum lipid profiles (mg/dl) 30-day after the administration of cinnamon extract and after 15-day wash-out period in male diabetic rats.

Parameter	FBG	TC	LDL	HDL	TG
1st group					
30 d	89.60±2.26[a]	85.60±2.13[a]	45.92±1.32[a]	36.80±2.10[a]	92.50±2.86[a]
45 d	90.10±2.10[a]	85.20±2.31[a]	45.92±1.53[a]	36.20±2.32[a]	91.99±2.91[a]
2nd group					
30 d	176.40±4.50[a]	109.60±2.07[d]	75.80±3.56[a]	30.10±2.28[a]	110.00±2.23[a]
45 d	192.20±3.96[b]	115.20±2.73[b]	82.10±1.30[b]	31.00±2.60[a]	126.60±2.88[b]
3rd group					
30 d	147.20±3.56[a]	87.60±2.50[a]	55.80±1.92[a]	30.00±2.16[a]	96.80±2.86[a]
45 d	163.40±1.81[b]	103.00±1.87[b]	70.60±0.54[b]	30.60±1.51[a]	113.00±2.54[b]
4th group					
30 d	152.80±4.49[a]	93.40±2.07[a]	59.87±3.70[a]	31.80±1.30[a]	100.60±1.81[a]
45 d	174.00±2.34[b]	108.80±1.92[b]	73.20±1.30[b]	31.60±1.34[a]	115.20±2.86[b]
5th group					
30 d	159.00±2.91[c]	103.60±2.88[c]	67.40±1.81[c]	34.20±2.28[c]	103.40±1.82[b]
45 d	175.80±4.02	107.20±3.11	70.00±0.54	35.30±1.58	116.80±2.68
6th group					
30 d	151.40±3.28[a]	94.00±2.54[a]	60.30±2.70[a]	31.90±1.48[a]	94.20±2.77[a]
45 d	175.60±1.51[b]	103.60±4.03[b]	70.10±2.96[b]	32.00±1.48[a]	118.80±1.30[b]

Values are expressed as overall means ± SD; n = 10 for each treatment group. [abcdef] Indicates values not sharing a common superscript letter were significantly different ($P < 0.05$) between 30 and 45 days. ([§]) FBG, fasting blood glucose; TC, total cholesterol; LDL, low density lipoprotein cholesterol; HDL, high density lipoprotein cholesterol; TG, triglycerides.

hyperglycemia, decreased insulin levels, polyuria and weight loss (Yadav et al., 2002; Song et al., 2003). In this context, it has been shown that sustained reductions in hyperglycemia decreases the risk of developing microvascular diseases and reduce associated complications (Gaster and Hirseh, 1998). Identification of foods, spices and other natural products that have an insulin potentiating factor (IPF) are important for improving glucose metabolism in diabetics and a more appropriate approach in terms of applicability and cost for diabetics in developing countries. Cinnamon in a spice and is used in food preparations for flavour and taste. The hypoglycemic effect of cinnamon is an additional benefit and is particularly important for type II diabetics (Safdar et al., 2004).

The present study was undertaken to assess the effect of different doses of cinnamon extract on body weight gain, food intake (FI), food efficiency ratio (FER), fasting blood glucose (FBG) and serum lipids profiles in alloxan diabetic rats. The data in Tables 1, 2 and 3 indicates that, the hyperglycemic effect of alloxan was associated with a significant decrease in the mean body weight gain, FI and FER compared to that in normal rats of negative control. These results are consistent those reporting that alloxan causes hyperglycemia and loss of body weight (Suresh and Das, 2006). The cinnamon mediated hyperglycemic effect observed after period I was associated with increase in body weight gain, food intake and FER compared to that in the positive control (PC) group. After period II, during which cinnamon extract administration was suspended, the mean FBG value gradually increased in all the groups, reaching levels similar to those in the PC group. This response in FBG was associated with significant drop in body weight gain, FI and FER during period II compared to the corresponding mean values of cinnamon extract-administrated diabetic rats and the positive control group during period I. Diabetic rats of the 3rd group, which were administered a dose of cinnamon extract at 200 mg/kg bw, exhibited the lowest mean FBG and highest weigh gain, FI and FER values during period II as compared to the corresponding mean values in the other groups and the PC group. These findings suggested that cinnamon extract has an insulin potentiating factor (IPF) which potentiates the effect of insulin in serum *via* increasing the pancreatic secretion of insulin from the existing β cells or its release from the unbound form. Cinnamon is mainly composed of several active ingredients including cinnamaldehyde

(Babu et al., 2007), cinnamic acid (Xiang, 1999), tannin (Inokuchi et al., 1984) and water soluble methylhydroxychalcone polymer (Jarvull-Taylor et al., 2001). Our findings are in agreement with previous reports indicating that cinnamon extract decreases blood glucose in Wistar rats (Qin et al., 2003). Hence, the observed anti-hyperglycemic activity for cinnamon extract could be associated with one or more of its components. Moreover, it has been shown that cinnamon increases the insulin sensitivity and glucose uptake in adipocytes (Jarvull-Taylor et al., 2001).

Our study indicated that the lowest dose of cinnamon extract (200 mg/kg bw) was the most efficient in lowering FBG and lipid indices in rats. Recently, several studies have provided as to the mechanism of action associated with cinnamon. In this context, both *in vitro* and *in vivo* studies have shown that cinnamon enhances glucose uptake by activating insulin receptor kinase activity, autophosphorylation of the insulin receptor, and glycogen synthase activity (Imparl-Radosevich et al., 1998; Jarvill–Taylor et al., 2001; Qin et al., 2003; Cao et al., 2007). Other recent studies have pointed out the ability of cinnamon to reduce lipid levels in fructose-fed rats, potentially via inhibiting hepatic 3-hydroxy-3-methylglutaryl CoA reductase activity (Lee et al., 2003).

Thus, cinnamon extract could have a great potential in clinical diabetes treatment, where it can be employed along with conventional diabetes treatment programmes. Indeed, it has been shown that supplementing the patient's conventional diabetes treatment plan with cinnamon capsules significantly lowered glycated hemoglobin (HbA1C), which is a form of hemoglobin that is measured primarily to identify the average plasma glucose concentration over prolonged periods of time (Crawford, 2009). However, a recent controversial report, based on meta-analysis conducted on five studies, has doubted the effectiveness of cinnamon extract concluding that cinnamon had no measurable effect on HbA1C, FBG and lipid concentrations (Baker et al., 2008). This highlights the need for further work to ascertain the biological activity of cinnamon extract.

The great potential and cost effectiveness associated with cinnamon have resulted in the initiation of a call for evaluation of effectiveness compared to other FDA approved oral anti-diabetic drugs (Fairman and Curtiss, 2009). As a natural herbal drug, which constitutes an essential component for complementary and alternative medicine (CAM), cinnamon extract offers a great potential as an insulin sensitizer in type II diabetes. More efforts are still needed to separate and identify the active principals responsible for this biological activity. In this context, the development of drugs based on herbal medicine has proved to be a very promising and cost-effective strategy. However, the development of herbal medicine requires tremendous research in order for it to meet strict criteria, such as those on standardization, quality control, safety, toxicity, and clinical trials (Buchanan et al., 2005). More importantly, elucidation of action mechanism of herbal medicines will turn CAM into 'evidence-based medicine' (Meijerman et al., 2006; Tascilar et al., 2006).

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