

Antidiabetic, antihyperlipidemic and antioxidant influences of the spice cinnamon (*Cinnamomum zeylanicum*) in experimental rats

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The present study investigates the effect of cinnamon (*Cinnamomum zeylanicum*) powder supplementation on glucose levels, lipid profiles, and oxidative stress parameters in alloxan-induced diabetic rats. Diabetes was induced in adult male Wistar rats via a single subcutaneous alloxan injection (15 mg/kg). Cinnamon powder was mixed with the standard feed of the rats in an amount of 5% for 28 consecutive days. Serum concentrations of total cholesterol (TC) and triglycerides (TG) were assayed at the end of the experimental period in all investigated groups. Anti-oxidative enzymes such as glutathione peroxidase (GPx), catalase (CAT) and superoxide dismutase (SOD) were sought in the serum and pancreas. Alloxan caused the fasting blood sugar level to increase. The administration of cinnamon blocked the increase of blood glucose. There was also a significant difference in the TG and TC levels between control and treated diabetic rats. In diabetic rats, cinnamon treatment restored the activities of SOD, CAT and GPx. These findings suggested that cinnamon has an anti-hyperglycemic effect, improves lipid profiles, and protect against damage induced by oxidative stress in the diabetic state.

Keywords: Cinnamon/extract/antidiabetic activity. Cinnamon/extract/antihyperlipidemic activity. Cinnamon/extract/antioxidant activity.

INTRODUCTION

Diabetes mellitus is a major disease around the world characterized by a serious, complex and chronic condition. This metabolic disorder affects approximately 4% of the population worldwide and is expected to increase by 5.4% in 2025 (Kim, Hyun, Choung, 2006). Diabetes mellitus, distinguished by hyperglycemia, is associated with disturbances in carbohydrate, protein and fat metabolism. Patients with diabetes mellitus have increased oxidative stress and impaired antioxidant defense systems, which appear to contribute to the initiation and progression of diabetes-associated complications (Maritim, Sanders, Watkins, 2003). The elevated glucose concentration directly injures cells and induces lipid peroxidation (Davi, Falco, Patrono, 2005). Alterations in antioxidant defense system enzymes such as catalase (CAT), glutathione peroxidase (GPx), superoxide dismutase (SOD) have

been demonstrated in diabetic patients (Maritim, Sanders, Watkins, 2003). Moreover, oxidative stress marker increases in pancreatic islets have been reported in experimental diabetic rats (Ihara *et al.*, 1999).

The induction of experimental diabetes in the rat using chemicals which selectively destroy pancreatic β cells is very convenient and simple to use. The most usual substances to induce diabetes in the rat are alloxan and streptozotocin. The understanding of changes in β -cells of the pancreas as well as in the whole organism after alloxan or streptozotocin treatment is essential for using these compounds as diabetogenic agents (Szkudelski, 2001).

The major mode of controlling diabetes can be achieved by diet, exercise and insulin replacement therapy (Pankaj, 2007). The use of hypoglycemic drugs, like insulin, biguanides, sulfonylureas and α -glucosidase inhibitors are accompanied by unpleasant side effects such as severe hypoglycemia, lactic acidosis, peripheral edema and abdominal discomfort (Ghorbani, 2013). Synthetic hypoglycemic agents produce serious side effects, whereas bioactive compounds derived from natural resources are regarded as safe and cost effective (Rao, Jamil, 2011). As reported by Aidi Wannas and Marzouk (2016), several

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plants have been traditionally recommended for the treatment of diabetes and the role of these plants in the management of diabetes has been determined by many studies. More than 400 plant species having hypoglycemic activity have been available in literature, however, searching for new antidiabetic, antihyperlipidemic and antioxidant drugs from natural plants is still attractive (Balamurugan, Nishanthini, Mohan, 2014).

Cinnamon (*Cinnamomum zeylanicum*) is an evergreen tree belonging to the *Lauraceae* family, traditionally harvested in Asian countries. It is one of the oldest herbal medicines mentioned in Chinese scripts as early as 4,000 years ago (Torizuka, 1998). The dried barks of Cinnamon are used to flavor or season various foods, and as a therapeutic agent for various diseases. Cinnamon is rich in essential oils and tannins. It possesses significant antidiabetic, antiallergic, antiulcerogenic, antipyretic and antioxidant properties (Kurokawa *et al.*, 1998; Dhuley, 1999; Dahankumar, Kulkarni, Rege, 2000; Khan, Safdar, 2003).

Due to the anti-hyperglycemic, anti-lipidemic and antioxidant properties of cinnamon, the aim of the present study was to evaluate the effect of cinnamon powder supplementation on abnormal glucose, lipid and antioxidant enzyme profiles in alloxan- induced diabetic rats.

MATERIAL AND METHODS

Animals

Adult male Wistar rats (190 g to 230 g) were used for the study. They were procured from Pasteur Institute of Tunis and maintained in the Faculty of Medicine of Tunis. The animals were individually housed under controlled temperature and hygienic conditions in polypropylene cages. Rats were maintained in an air-conditioned room (21±1 °C) with 12 h light: 12 h dark cycles. The relative humidity was maintained at 80%. They all received a standard pellet diet and water *ad libitum*.

The rats were allowed to acclimatize to the laboratory environment for 7 days before the start of the experiment. The standard diet contained 39.3% corn starch, 20% casein, 15.5% corn oil, 15.4% sucrose, 5% cellulose, 3.5% salt mixture, 1% vitamin mixture and 0.3% methionine. Throughout the study, rats were assessed weekly for body weight. All experimental procedures were conducted in conformity with institutional guidelines for the care and use of laboratory animals in Tunisia, and the international guidelines on the ethical use of animals (NIH publications No. 80-23).

Plant material

Cinnamon (*Cinnamomum zeylanicum*) dried barks were purchased on the Tunisian local market and they were botanically identified by Professor Abderrazek Smaoui (Biotechnology Center in Borj-Cedria Technopole, Tunisia). Then, Cinnamon dried barks were sorted and reduced to powder in a clean household blender. Conservation of the powder thus obtained was made in the absence of light and moisture. Cinnamon powder was mixed with the standard feed at a 5% rate.

Phytochemical screening

A qualitative phytochemical test to detect the presence of alkaloids, flavonoids, saponins, steroids, tannins, coumarins and phenols was carried out using standard procedures (Poongothai *et al.*, 2011; Yadav, Agarwala, 2011; Saxena, Sahu, 2012; Benmahdi *et al.*, 2012).

Induction of diabetes in experimental animals

Diabetes was induced in rats by an intraperitoneal injection of alloxan in a single dose of 15 mg/kg. Alloxan was dissolved in a freshly prepared 0.01 M sodium acetate buffer (0.154 M, pH 4.5) while control rats were injected with buffer alone (Raju *et al.*, 2001). Alloxan-injected animals were given 5% glucose (2 mL/kg body weight) at 12 h to prevent initial drug-induced hypoglycemic mortality. Blood was drawn from the tail plexus of conscious rats using a heparinized inoculator 7 days later.

Experimental design

The rats were randomly divided into four groups. Group I: control animals (n=6) receiving the standard diet. Group II: alloxan-diabetic animals (n=6) receiving standard diet. Group III: control animals given standard diet with cinnamon (n=6). Group IV: alloxan-diabetic animals given standard diet with cinnamon (n=6).

After 28 days, the animals were deprived of food overnight, sacrificed by decapitation, and then used in series of studies. Blood was collected from the jugular vein with heparin as anticoagulant and centrifuged at 1000 × g for 10 minutes to separate plasma (concerned at -20 °C). Assays were carried in plasma for triglycerides, cholesterol, serum proteins and enzymes of oxidative stress.

The body was cut open, and then the pancreas was removed and washed in ice-cold saline (NaCl 0.9% at 2 ± 2 °C). At a fraction of 0.4 g of pancreas, we added

4 mL of a solution of phosphate buffered saline (pH = 7.4), centrifuged at 3000 r/min for 30 min. The supernatant was collected and conserved at -80 °C for further investigations.

Glucose levels and lipid profile

Concentration of blood glucose was tested using a Diagnostic kit with test strips (On Call Advanced: Acon Laboratories, Inc.). Blood glucose was measured on the 7th, 14th, 21st and 28th days to assess the blood glucose-lowered effect of cinnamon. Rats with blood glucose at 2 g/L were considered diabetic. Protein level in plasma was determined by means of a colorimetric assay kit specific for total protein (Yacoubi *et al.*, 2011). The levels of protein were expressed in g/L. The serum concentrations of total cholesterol and triglycerides were determined using colorimetric kits (Henry, Cannon, Winkelman, 1979).

Antioxidant defense system assays

The activities of three antioxidant enzymes: SOD, CAT and GPx were determined in pancreas homogenate and in serum. SOD activity was measured according to the method of Beyer and Fridovich (1987), CAT activity was determined using the method of Aebi (1984) and GPx activity was measured according to the method of Flohe and Gunzler (1984).

RESULTS

Phytochemical screening

The phytochemical screening of cinnamon revealed the presence of alkaloids, coumarins, flavonoids, saponins, carbohydrates, steroids, tannins and phenols. However, proteins and glycosides were not detected (Table I).

TABLE I – Qualitative phytochemical screening of cinnamon powder

	Cinnamon powder
Alkaloids	+
Carbohydrates	+
Coumarins	+
Flavonoids	+
Glycosides	-
Phenols	+
Proteins	-
Saponins	+
Steroids	+
Tannins	+

Sign (+) indicates present and sign (-) indicates absent

Effect of cinnamon on body weight

Table II showed the average values of the body weight of different rat groups. All rats started the study with a comparable weight and no statistically significant difference ($P \leq 0.05$) was found between the four groups.

The rats in the control groups (groups I and III) showed a normal increase in weight over time. Cinnamon supplementation has no effect on the weight.

Alloxan-diabetic animals receiving standard diet (group II) showed a significant ($P \leq 0.05$) weight loss that continued until the end of the experiment at approximately 8%, 15% and 21.63% compared with initial body weight. At the end of the experiment, the average weight of alloxan-diabetic rats was statistically lower ($P \leq 0.05$) than controls.

For the group IV of diabetic rats receiving cinnamon, there was a significant loss ($P \leq 0.05$) of body weight. Compared with alloxan-diabetic rats that did not receive cinnamon, we found a significant increase ($P \leq 0.05$) in their body weight of about 1.2% (day 7), 5.55% (day 14),

TABLE II - Effect of cinnamon powder supplementation on body weight in normal and alloxan-diabetic rats

Groups [‡]	Weight (g) [†]				
	Day 0	Day 7	Day 14	Day 21	Day 28
Group I	214.2 ± 10.7 ^b	227.5 ± 6.9 ^b	239.3 ± 8.12 ^{ab}	251 ± 8.6 ^a	264.3 ± 10.2 ^a
Group II	217.5 ± 6.1 ^a	209.3 ± 6.8 ^b	203.5 ± 6.5 ^b	196.7 ± 5.09 ^{bc}	186.7 ± 10.2 ^c
Group III	205 ± 11 ^d	217.2 ± 10.4 ^c	227.5 ± 9.3 ^{bc}	238.7 ± 8.6 ^b	249.5 ± 8.3 ^a
Group IV	210 ± 11.4 ^b	211.8 ± 13.2 ^b	214.8 ± 10.3 ^b	216 ± 8.9 ^b	221.5 ± 10.3 ^a

[†]: mean values ± standard error, number of rats=6. [‡]: Group I: control animals receiving the standard diet. Group II: alloxan-diabetic animals receiving standard diet. Group III: control animals given standard diet with cinnamon. Group IV: alloxan-diabetic animals given standard diet with cinnamon. Different letters within each line indicate significant differences at $P \leq 0.05$ as determined by Duncan's multiple range tests.

9.81 % (day 21) and 18.64 % (day 28).

Effect of cinnamon on blood glucose

Table III represents the effect of cinnamon on the blood glucose profile of treated rats. Cinnamon did not alter blood sugar levels in control rats. Glucose profiles were nearly similar in rat groups I and III.

Furthermore, the treatment with alloxan caused a significant increase ($P \leq 0.05$) in blood glucose for rat groups II and IV from the beginning of treatment compared to the untreated rats (groups I and III). This increase was maintained throughout the experiment. Hyperglycemia was increased from 344.4 ± 35 mg/dL on the beginning to 353.7 ± 30.4 mg/dL on the 7th day and remained elevated on the other days of the experiment to reach 342.2 ± 23.9 mg/dL on the 28th day.

The cinnamon administration in diabetic rats caused an important and significant drop ($P \leq 0.05$) in blood glucose. The values significantly ($P \leq 0.05$) decreased from 337.2 ± 29.8 to 171 ± 18.7 mg / dl after 28 days of treatment. This effect was early manifested when cinnamon was administrated to rats.

Influence of cinnamon on lipid profile

Two lipid parameters were followed in this study: cholesterol and triglycerides (Table IV).

The induction of diabetes by alloxan led to an increase in plasma lipids levels. The triglycerides significantly ($P \leq 0.05$) increased from 0.41 ± 0.03 g/L at the beginning to 0.94 ± 0.27 at the end of experiment. The same results were shown for cholesterol: from 0.66 ± 0.16 to 0.90 ± 0.03 g/L ($P \leq 0.05$). These disturbances of lipid metabolism caused by diabetes were partially corrected by cinnamon.

Triglyceride levels were slightly decreased for the group III compared to group I when cinnamon was added. This difference was not statistically significant at $P \leq 0.05$. A significant reduction ($P \leq 0.05$) in cholesterol level was observed after administration of cinnamon for the group IV compared to the group II.

Antioxidant enzyme activities

The activities of SOD, CAT and GPx in pancreas are given in Table V. Results showed a significant reduction ($P \leq 0.05$) in the activity of SOD in the pancreas in untreated alloxan-diabetic compared to control rats from group I. The SOD activity significantly ($P \leq 0.05$) increased in the pancreas from 11.3 ± 1.2 U/mg of protein to 20.2 ± 3.4 U/mg of protein among alloxan-diabetic rats treated with cinnamon comparing to those not receiving cinnamon. Cinnamon administration to the group IV did not significantly change the activity of SOD in the pancreas at $P \leq 0.05$.

TABLE III - Effect of cinnamon powder supplementation on body glucose in normal and alloxan-diabetic rats

	Weight (g) †				
	Day 0	Day 7	Day 14	Day 21	Day 28
Group I	86.6± 3.6 ^a	88.6± 2.5 ^a	86± 2.4 ^a	88.1± 3.6 ^a	88.6± 4.8 ^a
Group II	344.4± 35 ^a	353.7± 30.4 ^a	308.5± 14.5 ^b	332.7± 20.7 ^a	342.2± 23.9 ^a
Group III	85.6± 3.6 ^a	87.6± 3.5 ^a	85.5± 4.5 ^a	84.4± 3.3 ^a	85.4± 7.3 ^a
Group IV	337.2± 29.8 ^a	249.7± 33.9 ^b	208.5± 25.6 ^c	186.6± 19 ^{cd}	171± 18.7 ^c

†: mean values ± standard error, number of rats=6. ‡: Group I: control animals receiving the standard diet. Group II: alloxan-diabetic animals receiving standard diet- Group III: control animals given standard diet with cinnamon. Group IV: alloxan-diabetic animals given standard diet with cinnamon. Different letters within each line indicate significant differences at $P \leq 0.05$ as determined by Duncan's multiple range tests.

TABLE IV - Effect of cinnamon powder supplementation on lipid profile in normal and alloxan-diabetic rats

Groups	Group I	Group II	Group III	Group IV
Triglycerides [g/L]	0.41±0.03 ^c	0.94±0.27 ^a	0.36±0.12 ^d	0.50±0.29 ^b
Cholesterol [g/L]	0.66± 0.16 ^c	0.90±0.03 ^a	0.58±0.12 ^d	0.77±0.30 ^b

Mean values ± standard error, number of rats=6. Different letters within each line indicate significant differences at $P \leq 0.05$ as determined by Duncan's multiple range tests.

The induction of diabetes in rats by alloxan provoked a significant reduction ($P \leq 0.05$) of the CAT activity of about 48.22% (from 50.6 ± 5 to 26.2 ± 2.9 mol H₂O₂ / min / mg of protein). An insignificant increase ($P \leq 0.05$) of the pancreatic CAT activity was observed in the group of control rats treated with cinnamon (group III) compared to normal rats (group I). Treatment of alloxan-diabetic rats with cinnamon caused a significant increase ($P \leq 0.05$) of 41.6% in the activity of pancreatic CAT compared to group II (from 26.2 ± 2.9 to 37.1 ± 4.9 mol H₂O₂/min/mg of protein).

In alloxan-diabetic rats, a significant increase ($P \leq 0.05$) of GPx was detected (0.6 ± 0.2 vs 2.3 ± 0.4 10⁻³ mM/min/mg) compared with the control rats. Cinnamon caused a significant elevation ($P \leq 0.05$) of GPx in alloxan-diabetic animals receiving cinnamon in contrast to those receiving normal diet. Supplementation of cinnamon caused a significant elevation ($P \leq 0.05$) of SOD, CAT and GPx in plasma of alloxan-diabetic rats (Table VI).

DISCUSSION

Diabetes mellitus, the most common endocrine disease, is not a single disease but a group of disorders. In fact, hyperglycemia, polyphagia, polydipsia and reduction

in body weight are frequently observed in the state of diabetes. In the present study, induction of diabetes by alloxan also produced a decrease in body weight. The cinnamon administration showed a significant increase of weight compared to diabetic control rats. Decrease in body weight of diabetic rats was possible due to catabolism of fats and protein, even though the food intake was more in diabetic rats than control. Due to insulin deficiency, protein content was decreased in muscular tissue by proteolysis (Vats, Yadav, Grover, 2004). Similar results were obtained by Mahmood *et al.* (2011) and El Desoky *et al.* (2012) who reported a decrease of weight in alloxan diabetic rats. As shown in this study, cinnamon was an effective agent contributing to the reduction of glucose levels in serum. The high serum glucose level induced by alloxan was decreased by the cinnamon powder supplementation for 50.02% during the fourth week of treatment ($p < 0.001$). Our results corroborated the findings of Mahmood *et al.* (2011) about the elevation of blood glucose level in alloxan-induced diabetic rats, and a reduction in this level after cinnamon extract administration. Rekha, Balaji and Deecaraman (2010) reported that the increased levels of plasma glucose in streptozotocin-induced diabetic rats were lowered by the administration of cinnamon extract. Mahera (2010) and Ping, Zhang and Ren (2010) reported that oral

TABLE V - Effect of cinnamon powder supplementation on the activity of SOD, CAT and GPx in the pancreas in normal and alloxan-diabetic rats

	SOD (U/mg of protein)	CAT (Mol H ₂ O ₂ /min/mg of protein)	GPx (10 ⁻³ mM/min/mg)
Group I	20.2 ± 2.5 ^b	50.6 ± 5 ^a	2.3 ± 0.4 ^a
Group II	11.3 ± 1.2 ^c	26.2 ± 2.9 ^c	0.6 ± 0.2 ^c
Group III	23.6 ± 2.6 ^a	51.5 ± 4 ^a	2.5 ± 0.4 ^a
Group IV	20.2 ± 3.4 ^b	37.1 ± 4.9 ^b	1.2 ± 0.2 ^b

Group I: control animals receiving the standard diet. Group II: alloxan-diabetic animals receiving standard diet. Group III: control animals given standard diet with cinnamon. Group IV: alloxan-diabetic animals given standard diet with cinnamon. Different letters within each column indicate significant differences at $P \leq 0.05$ as determined by Duncan's multiple range tests.

TABLE VI - Effect of cinnamon powder supplementation on SOD, CAT and GPx activities in plasma of normal and alloxan-diabetic rats

Groups	SOD (U/mL)	CAT (U/mL)	GPx (U/mL)
Group I	259.45 ± 6.325 ^a	3.96 ± 0.28 ^b	937.00 ± 37.12 ^c
Group II	158.45 ± 5.07 ^c	1.91 ± 0.26 ^d	764.62 ± 30.27 ^b
Group III	259.07 ± 7.10 ^a	4.46 ± 0.44 ^a	795.37 ± 318.34 ^a
Group IV	249.05 ± 13.37 ^b	3.82 ± 0.47 ^c	779.69 ± 312.50 ^{ab}

Group I: control animals receiving the standard diet. Group II: alloxan-diabetic animals receiving standard diet. Group III: control animals given standard diet with cinnamon. Group IV: alloxan-diabetic animals given standard diet with cinnamon. Different letters within each column indicate significant differences at $P \leq 0.05$ as determined by Duncan's multiple range tests.

administration of cinnamon essential oil significantly reduced the blood glucose level in diabetic rats which could be due to a reversal of insulin resistance or increasing insulin secretion by the regeneration of damaged pancreatic β -cells in alloxan-induced diabetic rats. Additionally, flavonoids are also known to regenerate the damaged β -cells in the alloxan-induced rats and act as insulin secretagogues (Alagammal, Agnel, Mohan, 2012). In this way, Anitha *et al.* (2012) reported that flavonoids, steroids, terpenoids and phenolic acids are known to be bioactive anti-diabetic components. According to Tacouri, Ramful-Babbolall and Puchooa (2013) and Pandey, Pandey and Singh (2014), these potent phytochemicals have been detected in cinnamon extract.

In diabetes, the levels of plasma lipids are usually raised and such an elevation represents a risk factor for coronary heart disease (Grundy, 1999). Also, an increase in levels of plasma cholesterol, phospholipids, free fatty acids and triglycerides was observed in alloxan diabetic rats. The abnormally high concentration of plasma lipids in diabetes is mainly due to the increase in the mobilization of free fatty acids from the peripheral depots, since insulin inhibits the hormone sensitive lipase (Dhandapani *et al.*, 2002). In the present study, there was a decrease in levels of triglyceride and cholesterol in diabetic alloxan rats treated with cinnamon. Blevins *et al.* (2007) reported that oral administration of cinnamon (20 mg/Kg body weight) significantly decreased serum total cholesterol, triglyceride levels and at the same time markedly increased plasma insulin. Amin and Abd El-Twab (2009) proposed that cinnamon extract may improve the postprandial overproduction of intestinal apoB48-containing lipoproteins by ameliorating intestinal insulin resistance and may be beneficial in the control of lipid metabolism. However, treatment with cinnamon essential oil significantly decreased and improved the diabetic status including protection of DNA against oxidative damage and hypocholesterolemic effect (Thresa, Christie and, Andrea, 2004). These results were in agreement with the study proposed by Anderson *et al.* (2004) which revealed that the polyphenols, polymers and anthocynins, found in cinnamon functions as antioxidants, potentiate insulin action and may be beneficial in the control of glucose intolerance and diabetes. Cao, Polansky and Anderson (2007) also reported that cinnamon extract and polyphenols improved the lipid profile of people with type 2 diabetes. On the other hand, our results showed a significant decrease in TG and TC levels in cinnamon-treated rats. Similar results were obtained by Qin *et al.* (2003) who reported that TG and TC were decreased by administration of cinnamon extract in rats treated with streptozotocin for 3 weeks.

Diabetes mellitus is strongly associated with oxidative stress, which can be a consequence of either increased production of free radicals, reduced antioxidant defense or both (Vijayalingam *et al.*, 1996). One of the most important therapeutic strategies for this disease is modulating insulin resistance and oxidative stress. The evaluation of oxidative stress can be monitored by several biomarkers. In this study, we choose to measure the activities of SOD, CAT and GPx which are known as protective enzymes against free radical formation in tissues. The induction of diabetes in rats by alloxan provoked a significant reduction of SOD, CAT and GPx levels in the pancreas. The treatment with cinnamon for four weeks significantly increased to near normal levels of SOD, CAT and GPx in the pancreas. These results revealed the protective role of cinnamon powder in decreasing lipid peroxidation and by normalizing antioxidant systems. Suganthi *et al.* (2007) evaluated a spice mixture of cinnamon for its effect on oxidative stress markers and antioxidant potential in tissues of high fructose-fed insulin-resistant rats. Administration of the spice mixture along with dietary fructose reduced the levels of peroxidation markers in tissues and improved the antioxidant status compared to rats receiving dietary fructose alone. Halvorsen *et al.* (2006) generated a ranked food table with values for total content of redox-active compounds and ground cinnamon ranked fourth with regard to total antioxidant content (17.647 mM/100 g).

CONCLUSION

Controlling the levels of glucose, cholesterol, triglycerides and activities antioxidant enzymes in rats treated with the cinnamon may be an encouraging result for an alternate treatment for diabetes.

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