

Original Research

Antioxidant Effects of a Cinnamon Extract in People with Impaired Fasting Glucose That Are Overweight or Obese

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Key words: cinnamon, antioxidants, glucose, diabetes, insulin

Objective: To determine the effects of a dried aqueous extract of cinnamon on antioxidant status of people with impaired fasting glucose that are overweight or obese.

Methods: Twenty-two subjects, with impaired fasting blood glucose with BMI ranging from 25 to 45, were enrolled in a double-blind placebo-controlled trial. Subjects were given capsules containing either a placebo or 250 mg of an aqueous extract of cinnamon (Cinnulin PF) two times per day for 12 weeks. Plasma malondialdehyde (MDA) concentrations were assessed using high performance liquid chromatography and plasma antioxidant status was evaluated using ferric reducing antioxidant power (FRAP) assay. Erythrocyte Cu-Zn superoxide (Cu-Zn SOD) activity was measured after hemoglobin precipitation by monitoring the auto-oxidation of pyrogallol and erythrocyte glutathione peroxidase (GPx) activity by established methods.

Results: FRAP and plasma thiol (SH) groups increased, while plasma MDA levels decreased in subjects receiving the cinnamon extract. Effects were larger after 12 than 6 weeks. There was also a positive correlation ($r = 0.74$; $p = 0.014$) between MDA and plasma glucose.

Conclusion: This study supports the hypothesis that the inclusion of water soluble cinnamon compounds in the diet could reduce risk factors associated with diabetes and cardiovascular disease.

INTRODUCTION

Rates of free radical formation are increased in obesity [1]. In people that are obese, the leading causes of oxidative stress have been identified as hyperglycemia, insulin resistance, increased tissue lipid levels, inadequate antioxidant defenses, enzymatic sources within the endothelium and chronic inflammation [2]. Conversely, oxidative stress is presently accepted as a likely causative factor in the development of insulin resistance which is present in obesity [3]. The mechanisms leading to the insulin cascade down-regulation in cells subjected to oxidative stress involves increased serine/threonine phosphorylation of insulin receptor substrate-1 (IRS1), impaired insulin-stimulated redistribution of IRS1 and phosphatidylinositol-kinase between cytosol and

low-density microsomal fraction followed by a reduced protein kinase-B phosphorylation and glucose transporter 4 (GLUT4) translocation to the plasma membrane. In addition, prolonged exposure to reactive oxygen species (ROS) affects transcription of glucose transporters, whereas the level of glucose transporter 1 (GLUT1) is increased, GLUT4 level is reduced [4]. Oxidative stress has been described as a key factor in obesity-related diseases such as diabetes [5], atherosclerosis [6,7] and inflammation [8]. In people that are overweight or obese, reducing oxidative stress by increasing antioxidant dietary intakes could be a possible method to reduce the incidence of these pathologies. Among dietary antioxidants, polyphenols have been linked with the hypothesis that their redox activities may confer specific health benefits [9,10]. In the dietary antioxidant group, polyphenols from cinnamon could

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be of special interest in people that are overweight with impaired fasting glucose since they might act both as insulin sensitizers and antioxidants. Aqueous extracts from cinnamon have been shown to increase in vitro glucose uptake and glycogen synthesis, increase phosphorylation of the insulin receptor and likely help trigger the insulin cascade system [11,12]. We have also reported that aqueous extracts from cinnamon enhance the in vitro activity of insulin [13]. In animal studies, dried aqueous cinnamon extracts potentiate insulin-regulated glucose utilization via enhancing insulin signaling [14] and prevent the insulin resistance induced by a high fructose diet in part by enhancing the insulin signaling pathway [15]. Cinnamon essential oil enhanced insulin sensitivity in Zucker fatty rats [16] and, recently, in db/db mice, anti-diabetic effects of cinnamon extracts on blood glucose were observed in relation with improved insulin sensitivity [17]. In patients with diabetes, cinnamon extracts have been reported to have beneficial effects in reducing fasting plasma glucose [18,19].

Given these findings, we hypothesized that polyphenolic polymers found in cinnamon, with insulin-like biological and antioxidant activities, [14] could improve plasma fasting glucose and oxidative stress markers in people at high risk of oxidative stress. Therefore, this work was designed to investigate in people that are overweight or obese, with impaired fasting glycemia, the effects of a twelve week supplementation of the dried aqueous extract of cinnamon on oxidative stress markers including plasma malondialdehyde (MDA) levels, plasma thiol (SH) group oxidation, FRAP (Ferric Reducing Activity Plasma), antioxidant erythrocyte enzyme activities as superoxide dismutase (Cu-Zn SOD) and glutathione peroxidase (GPx), and the possible correlation with fasting glucose and plasma insulin levels.

METHODS

Subjects

Twenty-two subjects were enrolled in a double-blind placebo-controlled trial. Subjects were recruited by posted announcements. There was one drop-out in the Cinnulin group. Subjects provided written and dated informed consent to participate in the study. Adult subjects were required to have fasting blood glucose between 100 mg/dL (5.6 mmol/L) and 125 mg/dL (6.9 mmol/L), a BMI between 25 and 45, have normal values for liver and kidney function tests, and be willing to maintain their usual dietary and physical activity habits. Subjects were excluded who were pregnant or lactating, or with any serious metabolic disorder including diabetes, thyroid diseases, or with a history of hepatorenal, musculoskeletal, autoimmune or neurologic disease. Subjects taking thyroid, hyperlipidemic, hypoglycemic, anti-hypertensive, anti-coagulant medications containing pseudoephedrine or other stimulants were excluded. In addition, subjects taking weight loss supplements or drugs within 30 days prior to the start of the study, who had gained

or lost more than 20 lbs within the past 30 days, who drank more than three cups of percolated coffee (or an equivalent amount of cola) per day, and who smoked or had quit smoking within the past six months were also excluded.

Groups

Subjects were divided randomly into two groups and given either a placebo or 250 mg of a dried aqueous extract of cinnamon (Cinnulin PF) two times per day for 12 weeks. Cinnamon capsules, containing a dried aqueous extract of Cinnamomum cassia were provided by Integrity Nutraceuticals, Inc. (Sarasota, FL). Integrity Nutraceuticals has a Cooperative Research and Development Agreement with United State Department of Agriculture (USDA) and RA Anderson.

Biological Parameters

Blood was collected after an overnight fast at the beginning of the study, after 6 weeks, and after 12 weeks in heparinized tubes protected from light and centrifuged at room temperature for 10 min at 3000 g. Plasma and erythrocyte pellets were immediately isolated, aliquoted and stored at -80°C until measurements were completed within 6 months.

Plasma thiol groups, which are markers of plasma protein oxidation, were assayed as described by Faure and Lafond [20]. The calibration was obtained from a stock solution of 100 mM N-acetyl cysteine (NAC) in the range of 0.125 to 1 mM. Standards and plasma samples were placed in 0.05 M phosphate buffer, EDTA 1 mM, pH 8, and bis-5,5'-dithio-bis-2-nitrobenzoic acid (DTNB), 2.5 mM, and absorbance measured at 412 nm.

Plasma MDA concentrations, which are markers of lipid peroxidation, were assessed using high pressure liquid chromatography (HPLC) as described by Richard *et al.* [21]. Plasma antioxidant status was evaluated using ferric reducing antioxidant power (FRAP) assay as a global marker of the antioxidant power. The FRAP assay uses antioxidants as reductants in a redox-linked colorimetric method. In this assay, at low pH, a ferric-tripyridyltriazine (Fe^{III} -TPTZ) complex is reduced to the ferrous form, which is blue and monitored by measuring the change in absorption at 593 nm. The change in absorbance is directly proportional to the reducing power of the electron-donating antioxidants present in plasma. The absorbance change is translated into a FRAP value (in $\mu\text{mol/l}$) by relating the change of absorbance at 593 nm of test sample to that of a standard solution of known FRAP value [22].

Erythrocyte Cu-Zn SOD activity, which is an antioxidant enzyme detoxifying oxygen radical species as superoxide O_2° , was measured after hemoglobin precipitation by monitoring the auto-oxidation of pyrogallol by the method of Marklund and Marklund [23]. Erythrocyte GPx activity, which is a selenoenzyme involved in protection against hydrogen peroxide OH° was evaluated by the modified method of Gunzler [24] using tertbutyl hydroperoxide (Sigma Chemical Co, Via Coger, Paris,

Table 1. Antioxidant Markers, Glucose, and Insulin Levels in Cinnamon Group vs. Placebo

Parameters	Cinnamon	Cinnamon	Cinnamon	Placebo	Placebo	Placebo
	0 week	6 weeks	12 weeks	0 week	6 weeks	12 weeks
Time of supplementation						
FRAP $\mu\text{Mol/L}$	812 \pm 38	874 \pm 52.4	918* \pm 33	707 \pm 58	709 \pm 60	660 \pm 54
Plasma MDA $\mu\text{Mol/L}$	2.7 \pm 0.2	2.4 \pm 0.1	2.2* \pm 0.1	2.4 \pm 0.1	2.40 \pm 0.1	2.5 \pm 0.1
Plasma SH groups $\mu\text{Mol/g prot}$	4.89 \pm 0.20	5.26 \pm 0.20	5.56* \pm 0.20	5.26 \pm 0.20	5.14 \pm 0.10	4.97 \pm 0.20
RBC Se-GPx U/gHb	41.3 \pm 2.80	41.5 \pm 2.60	41.86 \pm .70	45.68 \pm 3.10	46.67 \pm 3.40	46.2 \pm 3.40
RBC Cu ZnSOD U/mg Hb	1.17 \pm 0.05	1.15 \pm 0.1	1.20 \pm 0.1	1.30 \pm 0.05	1.27 \pm 0.03	1.37 \pm 0.05
Fasting Glucose mg/dL	114 \pm 2.2	115 \pm 6.8	102* \pm 4.3	112 \pm 3.2	109 \pm 5.7	113 \pm 4.6
Fasting Insulin pmol/ml	11.34 \pm 1.70	11.95 \pm 5.94	14.15 \pm 11.19	10.30 \pm 1.76	9.47 \pm 1.59	9.56 \pm 1.88

* Statistically significant at $p < 0.05$ between 0 and 12 weeks.

Data are for 11 subjects in the cinnamon group and 10 subjects in the placebo group at each time point.

France) as a substrate instead of hydrogen peroxide. Results are expressed as μmoles of NADPH (Boehringer-Mannheim).

Statistical Analyses

Data are expressed as mean \pm SEM. Wilcoxon signed ranks tests were used to compare all variables between baseline and at 6 and 12 weeks of treatment in the placebo and in the cinnamon groups. Statistical significance was set at $p < 0.05$. Data analyses were performed using the statistical software package (Statistica Program, Statistical Software, Paris, France).

RESULTS

Baseline age of the subjects in the placebo group was 45.8 ± 3.6 years with a BMI 34.2 ± 4.2 , and 45.6 ± 2.7 with a BMI of 32.3 ± 3.5 for the cinnamon group. Other baseline variables are shown in Table 1 with additional details of subjects in our previous study [25]. No significant changes were observed in the placebo group between the beginning and the end of the study (Table 1). In the cinnamon group, fasting glucose decreased from 114 ± 2.2 to 102 ± 4.3 mg/dL. Fasting insulin was not altered by the cinnamon supplementation. Plasma oxidative stress markers were all significantly improved ($p < 0.05$). Ferric Reducing Activity of Plasma (FRAP) and plasma SH groups increased, while plasma MDA levels decreased. Moreover, there was a positive correlation ($r = 0.74$; $p = 0.014$) between MDA and plasma glucose (Fig. 1). In contrast, RBC antioxidant enzymes, SOD and GPx, were not altered by the supplementation. In parallel with the hypoglycemic effects, the antioxidant effects of the treatment became significant after 12 weeks, but not after 6 weeks (Fig. 2).

DISCUSSION

Oxidative stress, which is increased in obesity, plays an important role in the development of diabetes and cardiovascular diseases in people that are obese [26]. The objective of this study was to determine whether oral administration of a

cinnamon extract would improve oxidative stress in people that are overweight or obese with impaired fasting glucose, and consequently be a possible nutritional approach in reducing the risk of diabetes, cardiovascular diseases and oxidative stress-related complications. Cinnamon, a natural product with a long history of safety, is rich in polyphenolic components that have been shown to improve the action of insulin in vitro [13], in animal studies [14,15] and to possess in vitro antioxidant activity [27]. In the present study, cinnamon extracts, at 500 mg/d for twelve weeks, decreased oxidative stress and improved impaired fasting glucose. Moreover, %fat mass decreased 0.7% for the subjects consuming the capsules containing the cinnamon extract and lean body mass increased 0.6 kg [25].

In the cinnamon group, impaired fasting glucose levels returned to normal physiological levels after twelve weeks of supplementation. This positive effect is comparable to a separate human study in which daily administration of 1000 mg of oral cinnamon extract reduced fasting glucose levels by 16 % over a 60 day study period in a prospective, randomized, placebo-controlled trial involving 60 subjects with type 2 diabetes mellitus [19]. A recent study also reported that cinnamon powder (3 g per day for 3 months) reduced by 10.3% the fasting plasma glucose in patients with diabetes mellitus type 2 [18]. We observed the hypoglycemic effects after 12 weeks of supplementation, but not after 6 weeks. The duration of the supplementation seems important to consider, since, in agreement with our data, a 6 week intervention with cinnamon supplementation (1.5 g/d) did not improve glycemic control in patients that were postmenopausal with type 2 diabetes [28].

The polyphenol type-A polymers extracted from cinnamon have been reported to stimulate autophosphorylation of the insulin receptor and inhibit protein tyrosine phosphatase (PTP-1). Both these mechanisms may lead to increased glucose uptake and glycogen synthesis [12,13]. Rats without insulin resistance, treated with oral cinnamon extract, also exhibited increased insulin sensitivity [14]. Cinnamon extract may potentiate insulin action via enhancing the insulin signaling pathways leading to increased PI 3-kinase activity, which regulates insulin-stimulated glucose uptake and glycogen synthesis. Cinnamon extract has also been found to mitigate insulin resistance

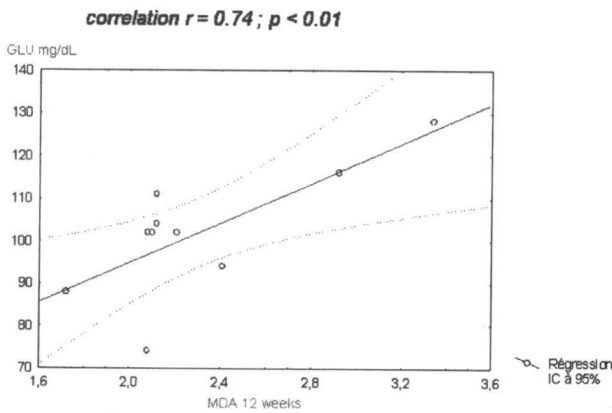


Fig. 1. Correlation between plasma MDA and glycemia after 12 weeks of supplementation.

as measured by the euglycemic clamp when induced by a high fructose diet in normal Wistar rats [15].

In this study, we found a positive correlation between plasma glucose levels and plasma MDA, a measure of lipid peroxidation. This observation confirms a previous study showing that plasma glucose levels play a role in determining oxidative status [29]. Impaired fasting glucose is a leading cause of oxidative stress and oxidative vascular complications in obesity and the improvement of impaired fasting glycemia in the cinnamon group is predictive of health benefits of cinnamon. Hyperglycemia causes the auto-oxidation of glucose, glycation of proteins, and the activation of polyol metabolism [30]. These changes accelerate the generation of reactive oxygen species and increase oxidative modifications of lipids and proteins [31]. The improvement of impaired fasting glycemia is associated with the antioxidant effects of cinnamon supplementation assessed by plasma MDA, SH groups and FRAP.

Obesity is an independent risk factor for plasma lipid peroxidation in humans [32] and poor glycemic control is an important factor in generation of protein oxidation [33]. Plasma MDA levels were reduced, indicating decreased lipid peroxidation, while plasma SH groups were increased, indicating a protection of SH groups against oxidation. The oxidation of lipids is thought to play a crucial role in the generation of atherosclerotic lesions in obese patients [34]. For patients suffering from obesity, cardiovascular diseases and diabetes, it is well-known that decreasing lipid peroxidation is an important health challenge to avoid oxidative damage of the arterial walls and oxidative complications [35]. Functional consequences of SH group losses include protein misfolding, catalytic inactivation and decreased antioxidative capacity [36]. In the group receiving cinnamon, plasma SH groups were increased after twelve weeks of supplementation, suggesting that cinnamon acts in protecting both lipids and proteins against oxidation. In parallel, the FRAP, which is a measure of the total antioxidant capacity of plasma, was increased thereby providing a contributory factor to the protective effects of cinnamon supplementation.

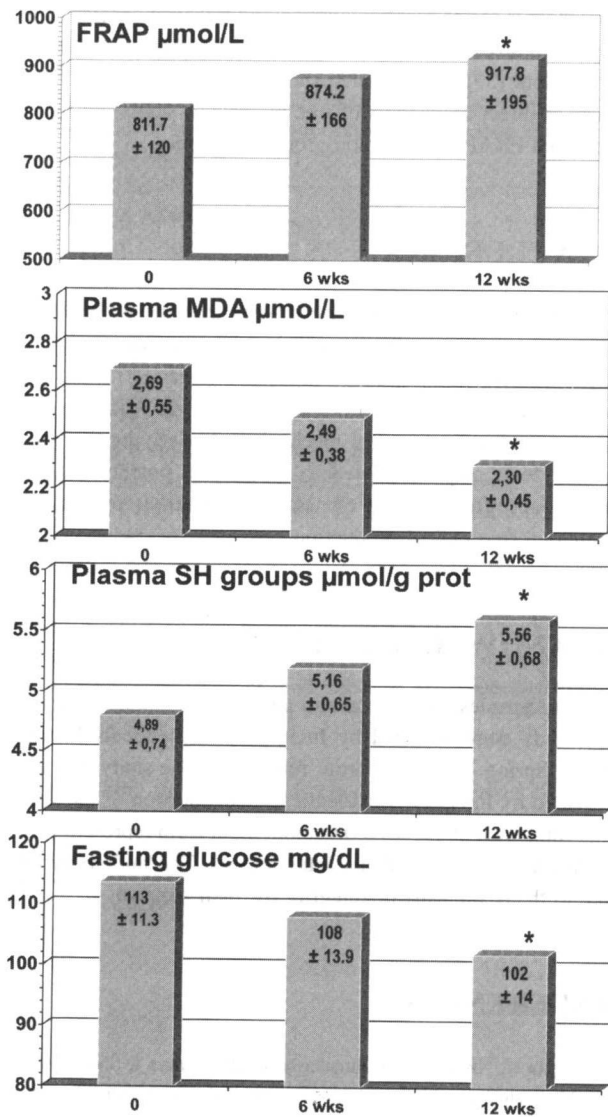


Fig. 2. Time-dependent improvements of the oxidative stress parameters.

In contrast, cinnamon intake did not alter the activity of the antioxidant enzymes in erythrocytes. Consistent with our findings, another study on polyphenols reported that, in humans, the polyphenols of red wine do not alter the activities of renal antioxidant enzymes, while plasma antioxidant capacity is enhanced following red wine consumption [37]. However, in rats fed high fat diet with species rich in cinnamon, antioxidant enzymes activities were found to be enhanced [38]. These discrepancies could be due to the different designs and duration of the studies.

The insulin-like effects of cinnamon extracts lead to the improvement of impaired glycemia and, given the hyperglycemia-induced free radical production, may be involved in the biochemical mechanisms underlying the antioxidant effects of the cinnamon supplementation. It is also well documented that

polyphenols act as reactive oxygen and nitrogen species scavengers, redox-active transition metal chelators and enzyme modulators [39] and complementary effects of cinnamon extracts as direct scavengers of free radicals as suggested by the increased FRAP in cinnamon group is possible.

CONCLUSIONS

This study supports the hypothesis that the inclusion of cinnamon extracts in the diet of people that are overweight or obese would reduce oxidative stress and impaired fasting glycemia which are risk factors associated with diabetes and cardiovascular disease. The mechanisms underlying the beneficial effects may be related to the insulin potentiating and antioxidant effects of the cinnamon polyphenols resulting in decreased free radical production.

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