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ScopeMed

Anti-diabetic and antioxidant effect of cinnamon in poorly controlled type-2 diabetic Iraqi patients: A randomized, placebo-controlled clinical trial

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ABSTRACT

Aim: To determine the effect of cinnamon on fasting blood glucose, hemoglobin (Hb) A1c, and oxidative stress markers in poorly controlled type 2 diabetes. **Patients and Methods:** A total of 25 type 2 diabetic patients of both sexes, aged 49.1 ± 6.0, treated only with hypoglycemic agent sulfonylurea (glibenclamide) were randomly assigned to receive either 1 g of cinnamon or placebo daily for 12 weeks. **Results:** A highly significant ($P \leq 0.001$) reduction (10.12%) of fasting blood glucose level after 6 and 12 weeks of treatment 10.12% and 17.4%, respectively, compared to baseline value and to placebo group at corresponding duration. Meanwhile, the value of glycosylated Hb reduced in cinnamon treated group by (2.625%) and (8.25%) after 6 and 12 weeks, respectively, although this reduction was non-significant compared to baseline value. Concerning the oxidative stress markers, the level of serum glutathione showed highly significant ($P \leq 0.001$) elevation after 12 weeks as compared to baseline value and placebo group at corresponding duration, malondialdehyde serum level decreased after treatment of diabetic patients with cinnamon resulted in highly significant ($P \leq 0.001$) reduction after 6 and 12 weeks compared to placebo group, but when compared to baseline value, there is a (15%) reduction only after 12 weeks of treatment which was considered highly significant ($P \leq 0.001$) change, Finally, administration of cinnamon to diabetic patients for 12 weeks resulted in significant ($P \leq 0.05$) elevation of superoxide dismutase level. **Conclusion:** Intake of 1 g of cinnamon for 12 weeks reduces fasting blood glucose and glycosylated Hb among poorly controlled type 2 diabetes patients, as well as, there is improvement in the oxidative stress markers, indicating the beneficial effect of adjuvant cinnamon as anti-diabetic and antioxidant along with conventional medications to treat poorly controlled type 2 diabetes mellitus.

KEY WORDS: Antioxidants, cinnamon, poorly controlled diabetes mellitus, type 2 diabetes

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is one of the most prevalent diseases worldwide and in Iraq, The WHO estimates a prevalence of 347 million people with diabetes worldwide in 2013 [1]. The prevalence is expected to double between 2005 and 2030 and the greater proportion of this increase would be in the low to middle-income countries of Asia, Africa and South America [2]. Despite advances in methods of diagnosis and treatment protocols, poorly controlled T2DM responsible for high incidence of morbidity that extensively disturbed the quality of life in addition to high expenditures each year [3]. Understanding of mechanisms underlies the pathogenesis of disease enable better targeting of changes that led to good glycemic control and improvement in overall outcomes.

Oxidative stress is the loss of the normal balance between prooxidants and antioxidants represent important implicated mechanism in the pathogenesis of diabetic complications [4], patients with type 2 diabetes are vulnerable to increase oxidative stress due to the excessive production of free radicals especially reactive oxygen species (ROS) and impaired antioxidant defense mechanism [5]. Poorly glycemic control leads to hyperglycemia which results in increased production of ROS which causes membrane damage due to peroxidation of membrane lipids and protein glycation [6]; for this reason, the targeting of oxidative stress is necessary in diabetic patients. Many studies have shown that the use of antioxidants, as well as herbal agents, might help control the oxidative stress [7]. The use of herbal medicinal plants especially those used in folk medicine for the treatment of diabetes is common in Iraqi diabetic patients, among these, the use of cinnamon [8].

Cinnamon is one of the most widely used spices in the food and beverage industry, worldwide has also been well recognized for its medicinal properties for a long time. Traditional medicine has used cinnamon extracts for ailments such as arthritis, diarrhea, and menstrual irregularities. The dry bark of cinnamon trees is

rich in botanical source of polyphenolics and has been used to improve general health and treat a variety of disease conditions including diabetes [9]. In addition to anti-diabetic properties, cinnamon is known to have anti-inflammatory, antibacterial, and antioxidant properties [10]. Cinnamon lowering effect of glucose level may be due to many mechanisms; many *in vitro* studies have showed that cinnamon increases glucose entry into cells by enhanced insulin receptor phosphorylation and the translocation of glucose transporter glucose transporter-4 (GLUT4) to the plasma membrane [11]. The active compound responsible is believed to be poly-phenolic compound [12]. Another possible mechanism that explains the hypoglycemic effect of cinnamon is an increase in the expression of peroxisome proliferator-activated receptor (PPAR) (alpha) and (gamma) receptors thereby increasing insulin sensitivity [13]. Furthermore, it has also been demonstrated that cinnamon possesses an inhibitory effect on intestinal glucosidases and pancreatic amylase. Ceylon cinnamon is the most potent inhibitor of pancreatic amylase and intestinal sucrase [14]. A clinical study has demonstrated its ability to delay gastric emptying as well as lowering the postprandial glucose level [15].

Thus, cinnamon considered an important anti-diabetic spice, and different studies involving cinnamon administration have produced contrasting results. The aim of this randomized, double-blinded clinical trial was to analyze the effect of cinnamon powder on fasting blood glucose, glycosylated hemoglobin A1c (HbA1c) and oxidative state in Iraqi patients with type 2 diabetes.

PATIENTS AND METHODS

A prospective, placebo-controlled randomized clinical trial was carried out on 26 patients with T2DM who attend the Specialized Center for Endocrinology and Diabetes-AL-Risafa, Directoratc of Health-Baghdad were enrolled in this study. The inclusion criteria: Patients with T2DM of both sexes on sulfonylurea (glibenclamide), with age range 40-65 years (49.1 ± 6.0), and have disease duration of 5-10 years. The exclusion criteria: They should not have other associated chronic diseases like liver and kidney disorders and cardiovascular complications. Patients who are pregnant and breast feeding are excluded. They should not be on insulin therapy or other anti-diabetic drugs, or on antioxidant drugs like aspirin, and any associated drugs should be considered. They should not taking other hypolipidemic agent; anti-inflammatory or non-steroidal anti-inflammatory drugs.

The patients treated previously with full maximum dose of sulfonylurea (glibenclamide) (15 mg/day) and kept on dietary control, but with poor glycemic control as evidenced by abnormal values of fasting plasma glucose (FPG) and glycated Hb; those patients are carefully evaluated while they are on their already established treatment program for DM control for 2 weeks before the randomization:

1. Group A includes 12 patients treated with placebo in capsule dosage form in addition to the already given oral hypoglycemic agent (glibenclamide) and dietary control, for 12 weeks.
2. Group B includes 13 patients treated with cinnamon powder 500 mg in hard gelatin capsule twice daily (1000 mg/day) in addition to the already given oral hypoglycemic agent (glibenclamide) and dietary control for 12 weeks. The cinnamon powder was obtained from local market and approved by Medicinal Plant Center-Baghdad, Iraq.

Sample Collection and Preparation

After 12 h fasting, blood samples were collected from all subjects by venepunture (10 ml), before starting drug treatment (as baseline samples) and then after 6 and 12 weeks of treatment to follow the changes in the studied parameters.

Blood samples were divided into two tubes, one heparinized tube (1 ml of whole blood used for HbAlc determination) and the other part was collected in plain tube, then centrifuged at 3000 rpm for 10 min at 4°C. after centrifugation and isolation of cellular fraction; the obtained plasma fraction was divided into three parts in Ependorff tubes and stored frozen until analysis performed.

Biochemical Assay Methods

Measurement of serum glucose level (FPG)

Serum glucose level was evaluated using a ready- made kit for this purpose, according to the method of Barham and Trendoer [16], which is based on enzymatic oxidation of glucose to form glucuronic acid and hydrogen peroxide, and the reaction of the later with phenol and formation of quinonimine was followed spectrophotomertically at 505 nm. Results were expressed as mmol glucose/l, based on comparison with a standard glucose solution treated with the same method.

Determination of glycated HbAlc

The variant HbAlc program utilizes the principles of ion exchange high-performance liquid chromatography for the automatic and accurate separation of HbAlc. Prepared samples are automatically injected into analytical flow path and applied to the cation exchange column, where the Hb is separated, based on the attraction of Hb to the column material. The separated Hb then passes through the flow cell of the filter photometer, where changes in the absorbance at 415 nm are measured. Samples are required to hemolyze the blood and remove Schiff base. Samples are first diluted with hemolysis reagent and then incubated at 18-28°C for a minimum of 15 min [17].

Measurement of serum Malondialdehyde (MDA)

MDA is a by-product of lipid peroxidation and its measurement is based on the reaction of thiobarbituric acid (TBA) with MDA forming TBA-2 MDA adducts. According to the standard method of Stocks and Dormandy [18], which is modified by Gilbert *et al*. [19]. The method included the addition of 1.75 ml of saline azide to 0.25 ml plasma. Then, the mixture was centrifuged and 2 ml of supernatant was mixed with 0.5 ml of

H_2O and 0.5 ml of 1% TBA in 0.05 M NaOH. The mixture was incubated in a boiling water bath for 15 min to achieve color development. The tubes were cooled under tap water and the extent of MDA production was estimated from the absorbance at 532 nm. MDA concentration was calculated using a molar absortivity coefficient of 1.56×10^5/M/cm and the results were expressed as μmol MDA/l.

Measurement of serum glutathione (GSH) levels

GSH contents (measured as total sulfhydryl groups) were measured according to the method of Godin *et al*. [20]. 0.5 ml of serum was mixed with 206 ml of 3 mM DTNB prepared in 0.1 M phosphate buffer (pH 8). The yellowish color chromophor formed was measured spectrophotometrically at 412 nm during 2 min, and the concentration of GSH was calculated using a standard curve use for this purpose.

Measurement of serum superoxide dismutase (SOD) levels

SOD is one of the most important anti-oxidative enzymes. It catalyzes the dismutation of the superoxide anion into hydrogen peroxide and molecular oxygen. The sensitive SOD assay kit utilizes WST-1 that produces a water-soluble Formazan dye upon reduction with superoxide anion. The rate of the reduction with a superoxide anion is linearly related to the xanthine oxidase activity and is inhibited by SOD. Therefore, the inhibition activity of SOD can be determined by a colorimetric method. Detection method-absorbance (450 nm).

Statistical Analysis

The results were expressed as a mean±standard deviation. Student's *t*-test for paired and unpaired sample and ANOVA test was used to examine the degree of significance, $P < 0.05$ considered significant and less than 0.001 considered highly significant.

RESULTS

Administration of cinnamon 1000 mg to diabetic patients resulted in highly significant ($P \leq 0.001$) reduction (10.12%) of fasting blood glucose level after 6 weeks of treatment compared to baseline value; the reduction in fasting blood glucose level was (17.4%) after 12 weeks of treatment which was also highly significantly ($P \leq 0.001$) compared to baseline value and to placebo group at corresponding duration [Figure 1].

At the same time periods, the value of glycosylated Hb reduced in cinnamon treated group by (2.625%) and (8.25%) after 6 and 12 weeks respectively, although this reduction was non-significant compared to baseline value, but it was in line with that of fasting blood glucose [Figure 2]; and both changes give clear indication about the glucose lowering effect of cinnamon in type 2 diabetic patients.

The level of serum glutathione, the natural antioxidant, increased significantly ($P \leq 0.05$) after 6 weeks in both placebo and cinnamon treated groups compared to baseline value, while only cinnamon treated group showed highly significant ($P \leq 0.001$) elevation after 12 weeks as compared to baseline value and in comparison to placebo group at corresponding duration [Figure 3].

Concerning the MDA serum level, treatment of diabetic patients with cinnamon resulted in highly significant ($P \leq 0.001$)

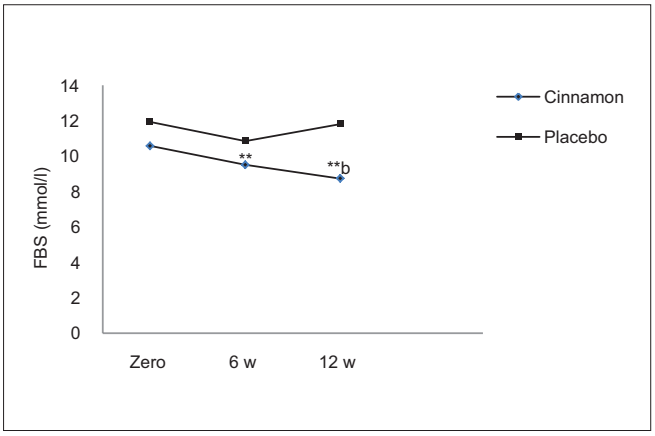

Figure 1: Effect of 1 g cinnamon powder on fasting blood glucose in diabetic patients. **Highly significant difference from baseline ($P < 0.001$). [b]Highly significant difference ($P < 0.001$) between cinnamon group and placebo group at corresponding duration

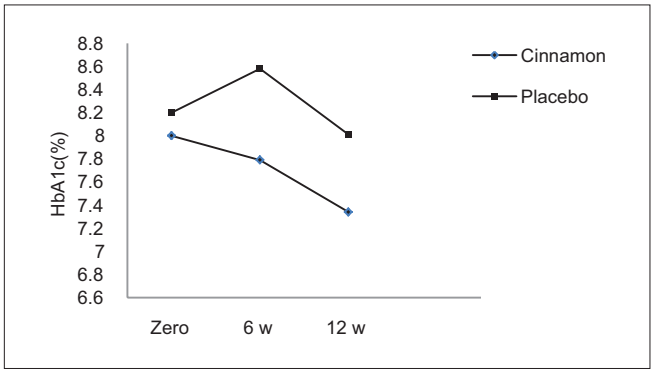

Figure 2: Effect of 1 g cinnamon powder on hemoglobin A1c % in diabetic patients

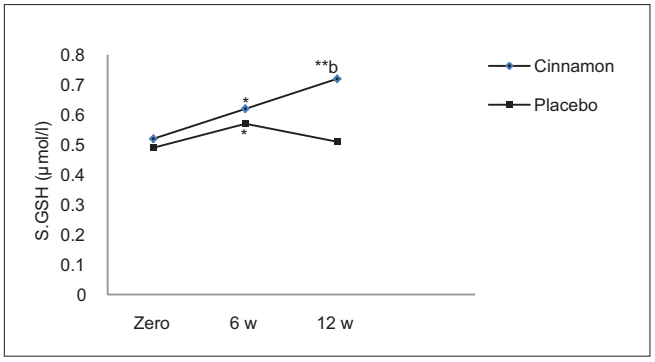

Figure 3: Effect of 1 g cinnamon powder on reduced glutathione serum level in diabetic patients. *Significant difference from baseline ($P < 0.05$), **Highly significant difference from baseline ($P < 0.001$). [b]Highly significant difference ($P < 0.001$) between cinnamon group and placebo group at corresponding duration

reduction after 6 and 12 weeks compared to placebo group, but when compared to baseline value, there is a (15%) reduction only after 12 weeks of treatment which was considered highly significant ($P \leq 0.001$) change [Figure 4].

Finally, results of this study showed that there was significant ($P \leq 0.05$) difference in the baseline level of serum SOD between placebo and cinnamon treated groups, in spite of that, administration of cinnamon to diabetic patients for 12 weeks resulted in significant ($P \leq 0.05$) elevation of SOD level [Figure 5].

DISCUSSION

This clinical trial demonstrates the hypoglycemic and antioxidant effects of 500 mg cinnamon powder twice daily in type 2 diabetic patients, the used cinnamon dose was tolerated well by patients, and there was no compliance. Khan *et al.* (2003) showed that administration of 1, 3 and 6 g per day of cinnamon improve blood glucose and lipid profile in type 2 diabetic people [21], and suggest that using cinnamon with a diet of diabetics may reduce incidence of risk factors associated with diabetes and cardiovascular diseases. Mang *et al.* demonstrated that administration of 3 g of cinnamon aqueous extract a day to type 2 diabetic

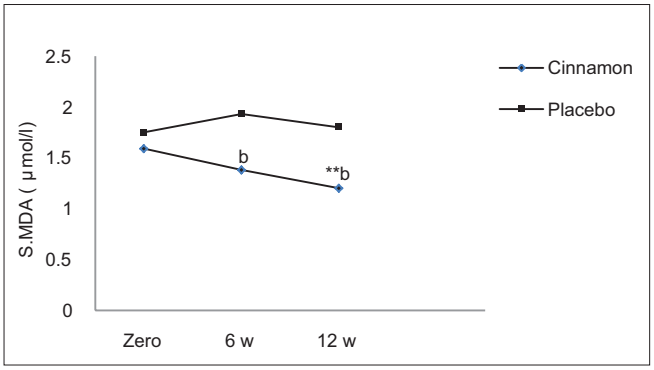

Figure 4: Effect of 1 g cinnamon powder on malondialdehyde serum level in diabetic patients. **Highly significant difference from baseline ($P < 0.001$). [b]Highly significant difference ($P < 0.001$) between cinnamon group and placebo group at corresponding duration

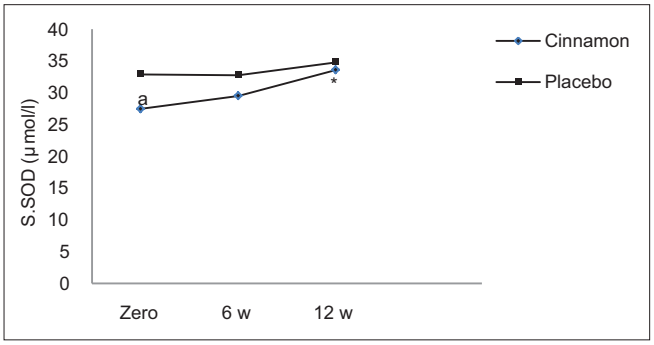

Figure 5: Effect of 1 g cinnamon powder on superoxide dismutase serum level in diabetic patients. *Significant difference from baseline ($P < 0.05$), [a]Significant difference ($P < 0.05$) between cinnamon group and placebo group at corresponding duration

patients on oral hypoglycaemic treatment resulted in significant reduction of the initial FPG values. However, the trial failed to demonstrate a significant lowering of HbA1C or plasma lipids [9]. Crawford showed that administration of 1g of cinnamon to diabetic patients for 90 days lowered the HbA1c by 0.83% as compared to 0.37% reduction in patients receiving usual care alone [22]. In a randomized, placebo-controlled double-blind clinical trial Akilen *et al.* studied the effect of cinnamon on diabetics on oral hypoglycemics by administering 2 g of cinnamon daily over a period of 12-week. The results demonstrated a significant reduction in HbA1c level. The study also demonstrated a significant reduction in blood pressure, FPG, body mass index and waist circumference at 12 weeks of treatment [23]. Other study done by Suppapitiporn showed the effect of cinnamon *cassia* powder in type 2 diabetics on oral therapy consisting of metformin or sulphonylurea in randomized, placebo-controlled clinical trial. After a 12-week period, HbA1c was decreased nonsignificantly in treated patients [24]. Recently, Anderson *et al.* found that diabetic individuals received cinnamon 500 mg/day for 2 months showing a significant decrease of both FPG compared the placebo control group, insulin sensitivity, assessed by homeostasis model assessment-insulin resistance, was also significantly improved by administration of cinnamon extract [25].

In this study, there is a highly significant reduction in fasting glucose level after 6 and 12 weeks of cinnamon use indicating the good glucose lowering effect of cinnamon powder while in placebo group there is no reduction a result which corroborate cinnamon effect. Many studies investigated the mechanism(s) of cinnamon as hypoglycemic agents, as reviewed by Medagama (2015); it may be due to its action at different levels of the insulin-signaling pathway [26]. Besides its action on insulin receptor phosphorylation and translocation of glucose transporter GLUT4 to the plasma membrane as mentioned above, studies showed that cinnamon administration increases the level glucagon-like peptide 1 [27,28]. Furthermore, cinnamon may increase the expression of PPAR and increasing insulin sensitivity [13]; Adisakwattana *et al.*, showed that cinnamon may be useful for the control of blood glucose level in diabetic patients through inhibition of intestinal α-glucosidase [14]; Anand *et al.* demonstrated that cinnamon inhibits gluconeogenesis and stimulate glycogen synthesis thus, improving glucose metabolism [29]; finally, cinnamon may delay the gastric emptying and caused reduction in post-prandial blood glucose [15].

Oxidative stress is one of the important factors in diabetes that plays an important role in vascular complications [30], evaluation of such changes markers may enable to determine the optimum time of targeting these changes. Nowadays, natural antioxidants are considered the preferred choice for the replacement of synthetic ones; these natural antioxidants can be formulated as food stuffs and can help prevent oxidative damage occur due to many diseases including type 2 DM [31]. It has been found that polyphenols, the natural dietary antioxidants found in cinnamon have been shown to reduce oxidative stress in a dose-dependent manner. Specific antioxidant

phytochemicals that have been identified in cinnamon include epicatechin, camphene, eugenol, gamma-terpinene, phenol, salicylic acid, and tannins [10].

Rao and Gan reviewed the antioxidant effects of cinnamon; they reported that cinnamon increased GSH level, also increase the activity of SOD [32]. In recent study, and Saifan showed that administration of cinnamon aqueous extract to obese diabetic rat resulted in improvement of activity of tissue antioxidant enzymes [33]. Finally, Roussel *et al*. show that administration of 250 mg of an aqueous extract of cinnamon 2 times per day for 12 weeks to subjects with impaired fasting blood glucose resulted in increasing the level of plasma thiol group while plasma MDA level decreased compared to that of placebo, they found that antioxidant effects were larger after 12 than 6 weeks [34]. The results obtained in this study showed that there is significant improvement in oxidative stress markers after 6 weeks, while highly significant increase in GSH level of diabetic patients after 12 weeks of cinnamon administration, at the same time, plasma MDA level highly significantly decreased after 12 weeks indicating the antioxidant effect of cinnamon in time-dependent manner.

CONCLUSION

In conclusion, administration of 1 g of cinnamon powder for 12 weeks reduces fasting blood glucose and glycosylated Hb among poorly controlled type 2 diabetes patients, as well as, increase the level of serum glutathione and SOD while reduces serum level of MDA, indicating the beneficial effect of adjuvant cinnamon as antidiabetic and antioxidant along with conventional medications to treat poorly controlled T2DM.

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