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Original Article

The Antioxidant and Anticoagulant Effects of Coumarin and Quercetin from Cinnamon Methanolic Extract, and the Assessment of Cinnamon Powder Effect on Plasma Parameters in Diabetes, and the Disinfectant Activity in Diabetic Patients

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Abstract

Background and Aim: This research tries to study the impact of cinnamon nutritional supplement on the blood glucose and lipid monitoring indicators in patients diagnosed with type II diabetes. The first aim of the present study was to evaluate the in vitro antioxidant and anticoagulant effects of flavones and coumarin from cinnamon methanolic extract (*Cin@m-Ext*). The second aim of this research was to study the impact of cinnamon powder capsule (*Cin@p-Cap*) on the beta cells of the pancreas in patients with type II diabetes.

Materials and Methods: This clinical trial was carried out on 160 patients diagnosed with type II diabetes. The 4 groups took edible capsules containing cinnamon (500 mg, 4 times daily). At the end of the intervention, a remarkable reduction in the fasting blood glucose was observed in the group receiving cinnamon comparing to the group taking a placebo.

Results: The results indicated a significant decrease of the blood clotting time in the presence of *Cin@m-Ext* in comparison with the control. A high-performance liquid chromatography (HPLC) procedure has been described to determine natural compounds in cinnamon methanolic extracts. Hence, it was concluded that the presence of high quercetin, ellagic acid and coumarin was influential in prolonging blood clotting in the intrinsic pathway. The antioxidant activity also indicated that *Cin@m-Ext* could be used as a potential radical scavenger, and also indicated that DPPH activity could increase in a dose-dependent manner.

Conclusion: These results indicated that the consumption of *Cin@p-Cap* might be useful in controlling and reducing the blood glucose levels by improving insulin sensitivity or reducing the rate of the absorption of carbohydrates in the small intestine among type II diabetic individuals.

Keywords: Herbal drug, Cinnamon, Anticoagulant, Flavones, Coumarin

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Introduction

Flavonoid compounds that are considered a significant class of plant polyphenols, are capable of having distinct physiological functions, and are plentiful in foods and the environment (1). They have a basic structural element, the flavan (2-phenylchromane) skeleton, and could be classified into different classes, namely flavonols (kaempferol, quercetin), flavan-3-ols (catechin) and flavones (luteolin) or flavanones (naringenin). As a subclass of flavonoids, quercetin is the richest flavonol found in cranberries, apples, blueberries, onions, black tea, red wine, and fruit juices (2). In plants, quercetin exists as glycosides, including quercetin-3-O-βD-glucoside (isoquercetin) and quercetin-3-rhamnosyl glucoside (rutin) (3).

The average daily consumption of quercetin is estimated to be 25 mg to 500 mg per day (11), and the use of dietary flavonols, including quercetin, and kaempferol at concentrations as high as 3000 mg/kg does not result in remarkable toxicity in animal studies and clinical trials. Quercetin could act on cardiovascular diseases (CVDs) by antioxidative action (4), hindering the proliferation and migration of smooth muscle cells (5), antihypertensive (6), anticoagulation and cardio protective actions (7). Hence, quercetin has widely drawn the attention of pharmacological researchers as a highly bio-active source with proven safety and cardioprotection (8).

Phenolic compounds are capable of having significant antioxidant activities pertaining to their abilities to scavenge free radicals, donate hydrogen, break radical chain reactions, and quench singlet oxygen (9). Some natural coumarins could be applied as human therapeutics. For instance, 4-hydroxycoumarins are used as microbial modifications. Moreover, they are very effective against aspirin and heparin as anticoagulants (10)

The content of phenolic compounds in biological samples could be determined by distinct analytical instrumental procedures, including gas chromatography (11), thin-layer chromatography (12), capillary electrophoresis (13) and high-performance liquid chromatography (HPLC). Natural compounds known as polyphenols that contain quercetin, coumarin, tannin, ellagic acid, glucose, hesperetin, cinnamomin, essential oil and resin are abundantly found in cinnamon. These compounds serve like insulin in the body and can contribute to the regulation of blood sugar levels, healthy circulation, and heart function (14). Due to the existence of tannin, it has the ability to stop diarrhea, and improve general body weakness. Moreover, its consumption helps stop bleeding (15). Cinnamaldehyde and trans-cinnamaldehyde (Cin) are the most significant compounds in its essential oil. Hence, it could be applied in various biological activities (16, 17). Procyanidins and catechins are found in cinnamon bark. The ingredients of procyanidins include both procyanidin A-type and B-type linkages (18, 19). These procyanidins that are extracted from cinnamon and berries also have antioxidant activities. Cinnamon has one of the highest antioxidant levels of any known spice. It could be reckoned a natural powerhouse containing antioxidants, anti-inflammatory and blood sugar-lowering abilities (20).

As previous studies have indicated, cinnamon might have a positive impact on the glycaemic control and the lipid profile in patients with diabetes mellitus type II. Some of the herbal plants have been used as traditional medicine for bleeding illnesses and to stop bleeding (21). This is mainly achieved by the use of anticoagulants, with heparins and coumarins being the most widely used one (22). As far as we know; however, the chemical constituents of Cinnamon methanolic extract that exhibits anticoagulant activity has not been investigated.

In this study, we investigated the in vitro anticoagulant actions of cinnamon methanolic extract (*Cin@m-Ext*) by assaying the coagulation time of prothrombin time (PT). This research indicated that the fractions of cinnamon methanolic extract contained high amounts of quercetin, ellagic acid and coumarin which are responsible for the anticoagulant activity. In the present study, the extraction and chromatographic HPLC conditions for polyphenolic analysis in the extract were examined. Further investigation led to the determination of the effects of cinnamon powder as a capsule (*Cin@p-Cap*) on insulin in a type II diabetic. Moreover, the disinfectant activity of cinnamon powder against diabetic patients was also investigated.

Materials and Methods

The Preparation of Cinnamon Methanolic Extract as an Anticoagulant Herbal Drug

Methanol was used to extract a powdered air-dried cinnamon plant. The crude methanol extract was produced by the maceration of plant material (10 g) with methanol (100 ml) and was left at rest (5 days, room temperature). The substance was filtered, and the obtained crude extract (*Cin@m-Ext*) was examined directly by HPLC-UV. This procedure was repeated in triplicate.

The Preparation of the Cinnamon Powder Capsule as an Anti-Diabetic Herbal Drug

The plant material samples of herbs of wild-growing cinnamon were collected from India and all the collected fresh samples were dried at room temperature in a well-ventilated room. The dried herbal drug samples were preserved in tightly closed bumper bags at room temperature in the absence of light. The doses of 500 mg of cinnamon powder were equally capsulated *(Cin@p-Cap)* as an anti-diabetic herbal drug.

In Vivo Anti-Diabetic Assay

This double blind clinical test was studied in Endocrinology and Diabetes Pardis Clinic in Shiraz, Iran, in 2017. A total of 160 individuals (80 males and 80 females) were selected to take a cinnamon powder capsule (each containing 500mg) four times a day (before breakfast and after breakfast, lunch and dinner) for 4 months. The inclusion criteria included the following: A) type II diabetic and having the age of 30-40 with the blood glucose range of 130-180 mg/dl, B) the same as group A but blood glucose over 200 mg/dl, C) the age of patients between 40-60 years old and the blood glucose range of 130-150 mg-dl and D) the same age as group C but the range of blood glucose over 200 mg/dl. The selected individuals were randomly assigned into two groups, namely the study and control groups. The present study had no advice for changing the medical care, diet, or exercise. The control group undertook the intake of placebo. The participants were recruited via e-mail announcements to clinic employees and also through an article in a local newspaper. A few tests, which are listed below, were performed on a patient to investigate the positive effects of cinnamon powder on insulin control.

Fasting Blood Glucose (FBG)

An examination of fasting blood glucose could provide us with information concerning how the body is managing blood sugar levels. Blood glucose reaches its peak roughly an hour after eating, and then declines. The instrument or auto analyzer pick 2 micro mL of serum and mix it with 100 micro ml of glucose reagent. After 15 min the result could be read on 500-550 nm.

Erythrocyte Sedimentation Rate (ESR)

The erythrocyte sedimentation rate (ESR) is widely acknowledged as a common hematological test which is carried out for the nonspecific detection of inflammation that might be induced by infection, certain types of cancers, and certain autoimmune diseases. It could be defined as the rate at which red blood cells (RBCs) sediment in a period of one hour. The process encompasses mixing the anticoagulated blood thoroughly, using Pasteur pipette, and filling the Wintrobe's tube up to '0' mark. There should be no bubbles in the blood (3). Subsequently, the tube should be vertically placed in the sediment reader stand and then left undisturbed for 30 min. Eventually, the result could be read.

Micro Albumin Test

Normal urine contains very little albumin. In pathologic conditions, as glomerular capillary wall permeability and/or filtration rate rise, albumin excretion and other macromolecules in urine increase. In an ordinary procedure, the entire components and samples must be at ambient temperature before use. The preparation of the plate with enough 8-well strips was carried out in order to test calibrators, controls, and samples in duplicate. Drop 10 ul of every calibrator, control, and samples into the relevant wells, and subsequently add 50 ul diluted enzyme conjugate reagent to every well. Then, mix it sufficiently and incubate it for 30 minutes at room temperature. Following the incubation, add distilled or deionized water to the wells and decant. Add 50 ul TMB Peroxide solution to every well. Subsequently, mix it well and incubate it for 15 minutes at room temperature. Add 100 ul stop solution to every well to stop the color development. Eventually, determine the absorbance for all the wells in an ELISA colorimetric analyzer at 450 nm.

In Vitro Coagulation Assay

The prothrombin time (PT) measures the extrinsic coagulation pathway and the common pathway (factors

prothrombin and fibrinogen). The effect of different concentrations (10, 20, and 50 µg) of *Cin@m-Ext* on prothrombin time was evaluated on coagulometer (Diagnostica Stago, Asnieres-sur-Seine, France) using reagents from Fisher Diagnostics according to the manufacturer's instructions.

In Vitro Antioxidant Activity

The antioxidant potential of the *Cin@m-Ext* was investigated through DPPH (1, 1-diphenyl-2-picrylhydrazyl) radical scavenging activity. All the tests were carried out in triplicate. Distinct concentrations of *Cin@m-Ext* (25, 50, 75 and 100 µg/ml) were mixed with equal volume of 0.1 mM DPPH solution. The reaction mixture was incubated in darkness at room temperature for 30 min, and then the absorbance was recorded at 517 nm. As a positive control, the ethanol (blank) and the ascorbic acid were used as the standard. The radical scavenging capacity of antioxidants is shown by the reduction in the absorbance of DPPH mixed reaction mixture after adding the antioxidant (23). The percentage of the inhibition or scavenging activity of free radicals was determined by the use of the following formula:

$$\%\ Scavenging\ activity = \left[\frac{\text{Values of optical density in control sample} - \text{Values in the experimental samples}}{\text{Values of optical density in control sample}}\right] \times 100$$

HPLC Analysis

To analyze polyphenol compounds in the cinnamon extract, high-performance liquid chromatography (Agilent technology 1200 series HPLC) was used. The instrument was equipped with a CO-2060 column oven, Bin pump sl De 63060570, and Tcc sl de 64156237 Dad detector. The detector was set at 285 nm. The chromatographic column was C18 (250×4.6 mm i.d.; Supelco, USA). The mobile phase was a mixture of methanol containing 5 µL H_3PO_4 at a flow rate of 1.5 mL.min-1. The column temperature was fixed at 40C°. The injection volume was 10 µL.

Statistical Analysis

The data have been depicted as the mean ± standard deviation, and the entire measurements and analyses were conducted in triplicate. Excel 2010 and SPSS V.18.0 statistical software were applied for the statistical and graphical assessments in the present research.

Results and Discussion

Type 2 diabetes includes two stages of safety and danger. The patient in danger stage is insulin-dependent. FBG test was conducted on two safety and danger groups, but micro albuminuria and ESR tests were conducted only for the danger group. The result of this study showed that *Cin@p-Cap* could increase insulin resistance by reducing blood glucose levels (Figure 1).

The Effects of Cinnamon Powder on Beta Cells of Pancreas

Our study indicated that 500 mg of *Cin@p-Cap* taken 4 times daily in the four groups (A, B, C and D) could decrease the fasting blood glucose (FBG) level and improve hyperlipidemia in human patients with type 2 diabetes as shown in Table 1a. The results indicated the existence of a high blood glucose level in the control group and at once a significant reduction in the case of *Cin@p-Cap* treated group. It seems that low levels of cinnamon have safe and control risk factors for diabetic patients.

The reduction in blood glucose levels reached the

Table 1: Results of (a) fasting blood glucose and (b) serum insulin level after 4-month intervention of *Cin@p-Cap* drug in four groups.

Group	FBG Level (mg/dl) (a)				
	Baseline	**First Month**	**Second Month**	**Third Month**	**Forth Month**
A	180±1.1	175±1.1	168±1.5	150±0.8	142±1.1
B	250±1.4	240±2.1	203±1.6	190±1.1	182±0.9
C	170±1.5	150±1.6	154±1.2	142±.3	113±1.2
D	208±0.9	192±1.4	170±0.9	183±0.9	175±1.1
	Insulin Level (mmol/L) (b)				
A	5±0.02	8±0.01	11.5±0.1	15±0.08	24±0.2
B	16±0.01	19±0.2	21±0.1	22±0.1	26±0.09
C	12±0.2	17±0.1	21±0.2	22±0.09	24±0.1
D	17±0.3	19±0.2	21±0.09	23±0.1	27±0.2

Table 2: Results of (a) ESR and (b) micro albumin level after 4-month intervention of *Cin@p-Cap* drug in four groups.

Group	ESR Level (µmL) (a)				
	Baseline	**First Month**	**Second Month**	**Third Month**	**Forth Month**
A	25±0.05	20±0.1	18±0.03	15±0.2	13±0.3
B	34±0.02	30±0.3	28±0.2	20±0.05	25±0.9
C	30±0.2	28±0.05	23±0.04	20±0.06	16±0.08
D	35±0.5	33±0.2	24±0.1	20±0.1	19±0.2
	Micro Albumin Level (mg/dl) (b)				
A	150±1.5	125±1.3	108±2.1	95±0.9	90±0.8
B	210±1.2	185±1.09	170±1.8	161±0.8	150±0.9
C	171±1.4	152±0.9	140±2.2	135±1.1	120±1.4
D	240±1.8	212±1.5	180±1.4	175±1.7	166±1.6

Table 3: The anticoagulant effect of *Cin@m-Ext*.

PT Level			
	Cin@m-Ext (µg)		
Baseline	**10**	**20**	**50**
12.08±0.1	13.38±1.1	17.20±0.4	28.51±1.2

Table 4: Antioxidant activity (DPPH free radical scavenging assay) of ascorbic acid and *Cin@m-Ext*.

	Scavenging activity %			
Samples	**25 µg/mL**	**50 µg/mL**	**75 µg/mL**	**100 µg/mL**
Cin@m-Ext (µg)	34.27 ± 0.06	54.26 ± 0.08	52.13 ± 0.05	61.21 ± 0.08
Ascorbic acid	32.16 ± 0.08	57.23 ± 0.02	66.34 ± 0.02	81.26 ± 0.05

highest level after 4 months and remained roughly constant after 2 weeks of *Cin@p-Cap* consumption. As shown in Table 1b, based on the calculated results of cinnamon's effect on insulin, insulin increases and the ability to metabolize rises resulting in a reduction of fasting blood glucose following an intervention of cinnamon capsule.

The decline of biochemical parameters following the intake of cinnamon is due to certain factors existing in cinnamon that potentiate the action of insulin in carbohydrate metabolism. Cinnamon contains polyphenolic polymers that might act as antioxidants, potentiate insulin action, and might be efficient in controlling glucose intolerance and diabetes. These determinants in cinnamon raise the reactivity potential of fat cells to insulin by activating the enzyme that causes insulin to join the cells (insulin-receptor kinase), and inhibits the enzyme that blocks this progression (insulin-receptor phosphatase) leading to the maximal phosphorylation of the insulin receptor, which pertains to increased insulin sensitivity (24). Cinnamon stimulates pancreas β-cells resulting in insulin secretion and the rise of insulin in the body. As a result, the body requires lesser glucose in the blood, and blood glucose decreases in the blood of the patient. On the other hand, the positive effects of cinnamon is due to interactions with insulin sensitivity and peroxisome proliferator-activated receptor gamma (PPARg), a regulator of adipogenesis. The main attempt is centralized on medicines that would serve as ligands for this receptor (25). Kim and Choung indicated that cinnamon could regulate insulin sensitivity via regulating PPAR-mediated glucose metabolism (26). Moreover, cinnamon bark extracts could inhibit the formation in vitro of advanced glycation end products (AGEs) that in turn could contribute to the emergence of diabetic complications. This inhibition was regarded to be caused by the capacity of phenolic compounds in the extracts to trap reactive carbonyl species (27).

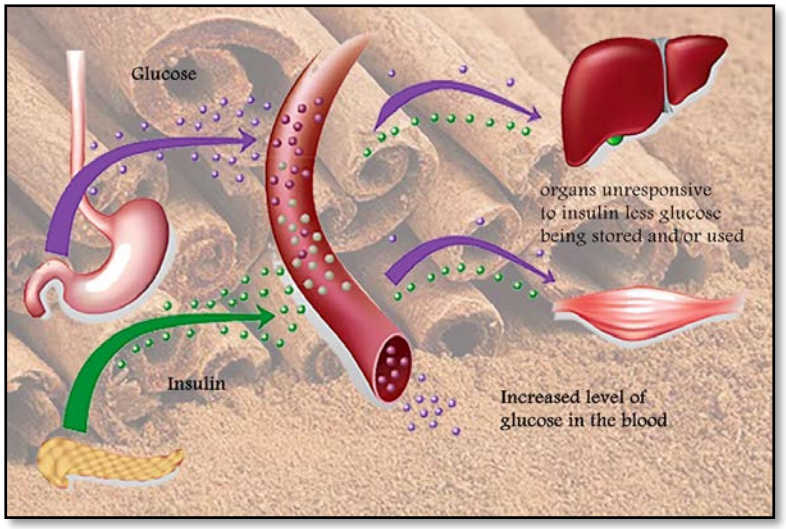

Figure 1. Schematic of insulin resistance by blood glucose reduction.

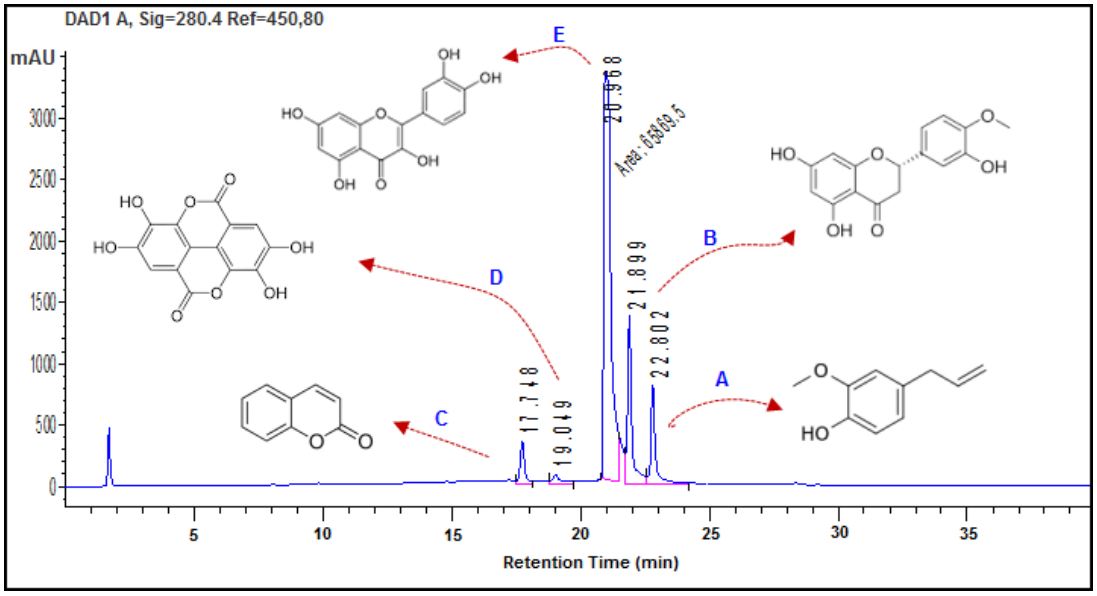

Figure 2. HPLC chromatogram of a polyphenolic compounds in cinnamon methanolic extract, Peaks: A: eugenol; B: hesperetin; C: coumarin; D: ellagic acid; E: quercetin.

The Effects of Cinnamon Powder on Inflammation and Micro Albuminuria

ESR test has indicated that 90% of the patients diagnosed with diabetes have a high blood pressure. The body of the patients diagnosed with diabetes is inflamed. Hence, a high volume of infections and waste materials are not refined in the kidneys. Consequently, infections occur in the body. It was observed in this research that cinnamon, due to its antibacterial and antimicrobial properties, was able to reduce the inflammation in the body which has been displayed in Table 2a. In fact, by the decrease in blood glucose and the rise in insulin production in the body, the blood pressure and body inflammation decrease and pressure on the kidneys drastically declines. Moreover, protein excretion highly decreases (microalbuminuria test). Consequently, the group of the patients (40 patients) were prescribed Ziptin pills that has similar effects. The comparison of the two groups revealed that cinnamon, with the same effect as Ziptin pills, could decrease the protein excretion of the patients of group II who had a high ESR.

On the other hand, when the pressure on the kidneys rises, urea and creatine rate of the blood increase incredibly. However, the intake of cinnamon in these patients and the results of microalbuminuria test (Table 2b) indicated that urea and keratin were in a normal level and lower rates of protein could be excreted.

The Effect of Cinnamon Extract on Blood Clotting as an Anticoagulant Drug

The present research was carried out to determine the impact of the active compounds of cinnamon plant on blood coagulation time. Likewise, in this in vitro study, the anticoagulant activity of *Cin@m-Ext* was evaluated by the conventional coagulation assay PT, and the results were summarized in Table 3. The HPLC chromatogram of cinnamon methanolic extract (Figure 2) showed very high levels of flavonols such as quercetin and ellagic acid at 280 nm (1070 and 228.37 mg/lit, respectively). Coumarin, eugenol and hesperetin were also identified comparatively in lower concentrations (77.1, 93. 2 and 31.57 mg/lit respectively). The results revealed that these major components are responsible for the anticoagulant activity. The polyphenolic from *Cin@m-Ext* possessed outstanding prolongation blood clotting time verified by the prothrombin time (PT). Hence, the components presented in HPLC chromatogram are able to inhibit fibrin polymers and clot formation, and degrade blood clot. These results, based on the laboratory study, indicate that quercetin and the flavone might control the coagulation via inhibiting the fibrinogenesis and coagulation determinants and the direct degradation of the blood clot.

The Assay of DPPH Radical Scavenging Activity

Cinnamon plant is considered as the most powerful antioxidant found in nature. It is highly efficient in the fight against aging and distinct ailments caused by reactive oxygen species. Cinnamon contains many polyphenols, particularly eugenol, ellagic acid and flavones that improves the body's defences, and neutralize the activity of free radical oxidation that are responsible for cellular aging and many other cases of cancer. Eugenol is a chemical which is found in many plants, herbs and spices, and is the best natural source of this powerful antioxidant. The antioxidant activity of *Cin@m-Ext* was investigated by DPPH scavenging as a free radical model, and was treated with various concentrations (25-100 µg/mL) of the tested samples.

The DPPH test is used in antioxidants to determine the activities of compounds with regard to scavenging free radicals. The method is according to the spectrophotometric determination of the DPPH concentration alteration caused by reacting with an antioxidant. There is a correlation between the reduction of the DPPH radical and the high scavenging activity which is exhibited by a particular sample. A gradual increase was observed in the scavenging or antioxidant activity with the rise in the treatment doses (Table 4). The DPPH is decolorized once DPPH receives an electron donated by an antioxidant compound from *Cin@m-Ext*. Consequently, it could be quantitatively measured by the alterations in absorbance.

Conclusion

In the present study, the HPLC analysis of different bioactive natural compounds, including quercetin, ellagic acid, coumarin, eugenol and hesperetin were identified that were influential in excellent antioxidant and anticoagulant activities, particularly prolonging blood coagulation, as exhibited by the cinnamon methanolic extract. Furthermore, this research demonstrated the positive impacts of cinnamon powder on insulin activity suggesting a possible role of cinnamon that stimulates pancreas β-cells leading to insulin secretion and insulin rise in the body.

We indicated that cinnamon powder capsule, taken 4 time daily (each time 500 mg) for a 4-month period could reduce the mean fasting serum glucose (17–27%), increase the insulin level (10-16%), decrease the ESR level (11-16%), and more importantly reduce creatinine and protein excretion in urine (15-21%). Hence, it could be concluded that the health benefits of cinnamon supplementation in type 2 diabetic patients that have been proposed so far could improve certain biochemical factor levels. Diabetes patients who use cinnamon in their food preparations regularly, might be able to maintain their fasting blood sugar levels and lipid profiles close to the normal levels. Hence, cinnamon is potentially efficient in pharmaceutical and biomedical applications. However, further studies are required to isolate pure bioactive compounds responsible for these activities with their mechanisms of action.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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