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Potential role of cinnamon in the prevention and management of diabetic vascular complications in humans

Mina Wassef Girgiss[1], Wassef Girgiss Nicola[2], Dawoud Fakhry Habib[3], Eman Refaat Youness[3], Nadia Mohamed Ahmed[3]and Mohamed Elsayed Elnemr[4].

[1]Department of Complementary Medicine, Medical division, National Research Centre (NRC), Cairo**, Egypt**.
[2]Department of Internal Medicine, Medical division, NRC, Cairo, **Egypt.**
[3] Medical Biochemistry Department, Medical division, NRC, Cairo**, Egypt.**
[4]Department of Internal Medicine, Faculty of medicine, 6th October University, **Egypt.**

***Correspondence:** mwgnicola@hotmail.com **Accepted:** 28 Jan. 2018 **Published online:** 24 Mar. 2018

Experimental and human studies proved cinnamon to have some biological activities like those of insulin hormone. It increases glucose uptake by the different cells and increases glycogen storage. It targets PPAR α and γ nuclear receptors which affect lipid and carbohydrate metabolism. Also it possesses antioxidant effects. We aim to study the effect of cinnamon on the vascular tree in obese type 2 diabetic patients. Sixteen obese type 2 diabetic female patients, each of them was given 1.8 gm of cinnamon powder in capsule form daily in three divided doses for three weeks. Their fasting serum paraoxonase-1, malondialdehyde, total cholesterol, LDL, HDL, Apo C II and Apo C lll were estimated before and after three consecutive weeks of cinnamon intake.Cinnamon significantly increased paraoxonase-1 and reduced malondialdehyde. It reduced total cholesterol, LDL cholesterol and increased HDL cholesterol. Again, it significantly reduced Apo C ll and decreased Apo C lll.In Conclusion cinnamon can be used as a supplementary agent in the management of atherosclerotic risk conditions such as obesity, type 2 diabetes mellitus, hypertension and dyslipidemia. Cinnamon tackled several important facets in the process of atherogenesis. It improved the oxidative stress, the lipid profile and the inflammatory state.

Keywords: Cinnamon, Type 2 diabetes mellitus, Paraoxonase-1, Malondialdehyde, Cholesterol, Apo Cs, Vascular tree.

INTRODUCTION

Some reviews reported the presence of a bioactive compound in cinnamon extract (CE), namely (CE; doubly linked procyanidin type-A polymer). Experimental studies on this compound, proved it to have biological activities akin to those of insulin hormone (Anderson et al., 2004). It increases glucose uptake through the activation of insulin receptors in the different cells by increasing the process of autophosphorylation; at the same time it lowers the tyrosine phosphatase enzyme activity which blunts insulin action (Imparl-Radosevich et al., 1998; Qin et al., 2003). Besides, it decreases insulin resistance and encourages glycogen storage through enhancing the glycogen synthase activity (Qin et al., 2003; Qin et al., 2004). Studies of CE on healthy volunteers and type 2 diabetic patients, showed encouraging results on both insulin action and blood glucose level.

This compound is claimed to act as a ligand for both peroxisome proliferator activated receptors (alpha and gamma) (PPAR α and PPAR γ). These nuclear receptors are involved in lipid and carbohydrate metabolism. The concomitant activation of both PPAR alpha and gamma

receptors improve insulin sensitivity without increasing body weight which occurs when PPAR gamma agonists are used alone (Qin et al., 2004; Sheng et al., 2008).

Moreover, cinnamon has been claimed to have antioxidant properties (Anderson et al., 2004; Dugoua et al., 2007). However, studies on cinnamon to elucidate an effective therapeutic mechanism on the vascular tree are lacking.

On the other hand, clinical studies on cinnamon powder showed much variations including, the selected samples of patients, dose of cinnamon ingested and the duration of ingestion. Besides, the results are conflicting concerning the blood glucose level, fasting insulin level, insulin resistance and serum lipid profile. In addition, most studies are small, of short duration and non-conclusive. Like in case of cinnamon extract, the effect of cinnamon powder on the vascular tree is lacking too (Power and Pratley, 2012).

AIM OF THE PRESENT WORK

To study the effect of cinnamon powder on some parameters which might have an impact on the vascular tree? These include: paraoxonase-1 (PON-1) as antioxidant agent and malondialdehyde (MDA) as an oxidative stress factor. Serum lipids including total cholesterol, LDL and HDL which are usually involved in atherogenesis. Also apolipoproteins C11 and C111 (Apo C11 and Apo C111) as inflammatory markers.

MATERIALS AND METHODS

Subjects:

Sixteen type 2 diabetic female patients aged 45 to 68 years of age, were selected from the diabetes outpatient clinics of the governorate hospitals. These constitute the subjects of this study and were selected according to the following criteria:

Inclusion criteria:

Type 2 diabetic females, middle aged or above, hyper tensives or not, overweight (BMI 25 < 30) or obese (BMI ≥30), not under anti lipidemic drugs.

Exclusion criteria:

These patients were free from endocrine disorders, metabolic diseases, not going on contraceptive pills or under hormonal treatment. They had no local or systemic infection (skin, chest, intestinal or urinary tract). They had no malignancy or any organ failure (heart, lung, liver or kidney).

Ethical committee approval:

This work has been approved by the Egyptian National Research Centre (NRC) ethical committee. Certificate number 150ll.

Consent:

All patients gave their written consent to be enrolled in this study.

Methods:

Each patient ingested 2 capsules of cinnamon powder thrice daily for three weeks. Each capsule contained 300 mg i.e. a total of 1.8 gm daily. The dose has been chosen empirically after reviewing the literature. In the literature several authors used different doses ranging from 1, 3, 6 gm of cinnamon daily (Khan et al., 2003).
Every patient was subjected for full history, thorough clinical examination and the following laboratory investigations before and after the course of cinnamon ingestion.

Laboratory Investigations

Determination of Paraoxonase 1 activity

Paraoxonase 1 activity was determined spectrophotometrically using phenylacetate as a substrate. Aryl esterase/ paraoxonase catalyze cleavage of phenyl acetate into phenol that is measured at wavelength 270 nm at 25˚C. The working reagent consisted of 20 mM Tris/HCl buffer, pH 8.0, containing 1 mM CaCl2 and 4 mM phenyl acetate as the substrate. Samples diluted 1:3 in buffer are added and the change in absorbance is recorded following a 20 sec lag time. Absorbance at 270 nm was taken every 15 s for 120 s. One unit of arylesterase activity is equal to 1 μM of phenol formed per minute. The activity is expressed in kU/L, based on the extinction coefficient of phenol of 1310 M−1·cm−1 at 270 nm, pH 8.0, and 25˚C. Blank samples containing water are used to correct for the spontaneous hydrolysis of phenylacetate (Higashino et al., 1972; Watson et al., 1995).

Determination of lipid peroxidation

Fasting serum lipid peroxidation products were measured by assaying the level of malondialdehyde. Serum malondialdehyde was measured spectrophotometrically after the method of (Ruiz-Larrea et al. 1994).

Determination of total cholesterol, HDL and LDL

Fasting serum total cholesterol was measured enzymatically after the method of (Trinder, 1969). Randox kit was used. Randox laboratories limited, 55 Diamond Road, Crumlin, Country Antrim, BT 29 4QY, United Kingdom.

Fasting serum HDL cholesterol was estimated by differential precipitation of apolipiprotein B-containing lipoproteins (VLDL, HDL and (a) Lpa) by phosphotungestic acid, sedimentation of the precipitant by centrifugation. HDL was subsequently estimated colorimetrically in the clear supernatant by an enzymatic method after (Burstein et al., 1980). Kit used of Cormatest from Linear Chemicals S.L. Joaquim Costa 182 pianta 08390 Montagat, Barcelona, Spain.

Fasting serum LDL cholesterol was calculated using the Friedewald formula as follows:

LDL-Cal (mg/dl) = TC–HDL-C–TG/5 (Anandaraja et al., 2005).

N.B.: Quantitative estimation of fasting serum triglycerides was done spectrophotometrically after Fossati enzymatic method (Fossati 1982), using the kit from Centronic Germany.

Determination of Apo C II

Fasting serum human Apo C II was estimated using the ELISA technique after Hatters *et al.,* (2000). Kit used from Assaypro LLC 3400 Harry S Truman P LVD St. Charles, MO 6301.

Determination of Apo C III

Fasting serum human Apo C III was estimated using the ELISA technique after Jong et al., (1999). Kit used Elabscience from Elabscience Biotechnology Co. Ltd. Address: Building 4, Room 401, Guandong Science and Technology Industry Park, Wuhan, PRC.

Statistical methods:

The collected data were coded, tabulated, and statistically analyzed using IBM SPSS statistics (Statistical Package for Social Sciences) software version 16.0. Descriptive statistics were done for quantitative data as minimum& maximum of the range as well as mean ± SD (standard deviation) for quantitative parametric data. Inferential analyses were done for quantitative variables using paired t-test in cases of two dependent groups with parametric data. The level of significance was taken at P value <0.05 is significant, otherwise is non-significant.

RESULTS

The mean fasting serum level of paraoxonase 1 (PON 1) significantly increased after cinnamon intake from 106.97 ± 41.14 mU/ml to 202.34 ± 131.16 mU/ml with P 0.016 while mean fasting serum malondialdehyde (MDA) decreased from 859.91 ± 293.05 nmol/ml to 769.49 ± 237.33 nmol/ml with P = 0.37 table (1) and figure (1).

Both mean fasting serum total cholesterol and mean fasting serum LDL decreased after cinnamon intake from 192.88 ± 83.89 mg/dl to 183.53 ± 50.44 mg/dl and 147.04 ± 80.71 mg/dl to 123.06 ± 48.46 mg/dl respectively, with P values 0.59 and 0.18 respectively, table (1) and figure (2). Mean fasting serum HDL on the other hand increased from 31.90 ± 19.08 mg/dl to 39.65 ± 14.88 mg/dl with P = 0.115 table (1) and figure (2).

Table (1): shows the values of the different parameters used before and after the period of cinnamon ingestion including: Paraoxonase 1 (antioxidant), Malondialdehyde (oxidative biomarker), total cholesterol, LDL, HDL, Apo C II and Apo C III.

		Before		After				
	N	Mean	SD	Mean	SD	Mean Diff	t	#P
Paraoxonase 1 (mU/ml)	14	106.97	41.14	202.34	131.16	-95.37	-2.74	0.016*
Malondialdehyde (nmol/ml)	16	859.91	293.05	769.49	237.33	90.42	0.92	0.370
Total Cholesterol (mg/dl)	16	192.88	83.89	183.53	50.44	9.35	0.54	0.596
LDL (mg/dl)	16	147.04	80.71	123.06	48.46	23.98	1.39	0.184
HDL (mg/dl)	16	31.90	16.08	39.65	14.88	-7.75	-1.67	0.115
ApoCII (ug/ml)	16	71.41	18.09	54.31	17.58	17.10	4.66	0.000*
ApoCIII (ng/ml)	16	13.90	6.11	13.08	7.52	0.82	0.38	0.711

N=16 , #P-value of paired t-test, *Significant

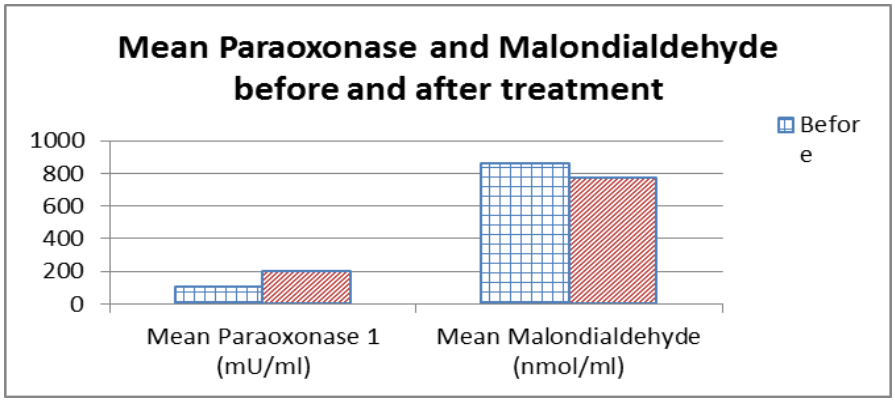

Figure (1) : shows significant increase in the mean fasting serum level of the antioxidant paraoxonase 1 (PON 1) from 106.97 ± 41.14 mU/ml to 202.34 ± 131.16 mU/ml; and a decrease in mean fasting serum level of the oxidative biomarker malondialdehyde (MDA) from 859.91 ± 293.05 nmol/ml to 769.49 ± 237.33 nmol/ml after cinnamon treatment.

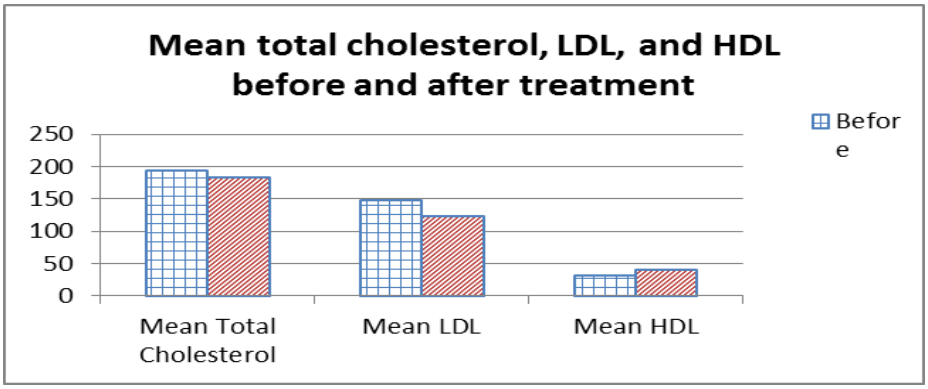

Figure (2) : shows a decrease in mean fasting serum total cholesterol and mean fasting serum LDL after cinnamon intake from 192.88 ± 83.89 mg/dl to 183.53 ± 50.44 mg/dl and 147.04 ± 80.71 mg/dl to 123.06 ± 48.46 mg/dl respectively; and an increase in mean fasting serum HDL from 31.90 ± 19.08 mg/dl to 39.65 ± 14.88 mg/dl after cinnamon ingestion period.

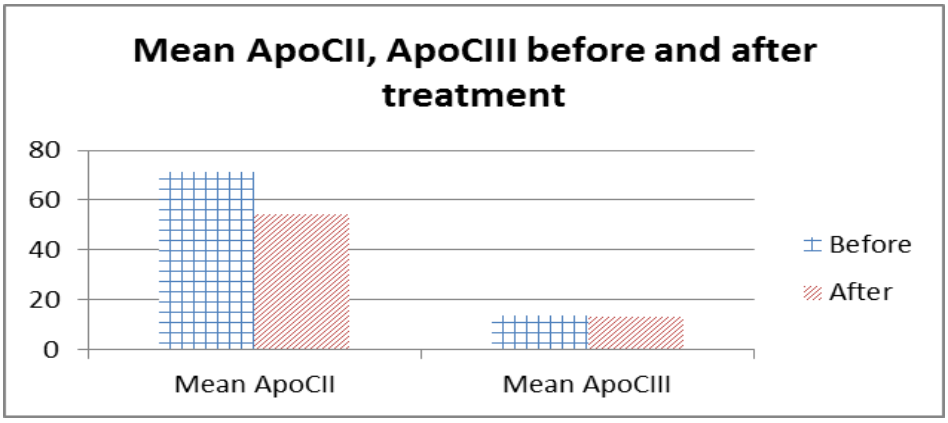

Figure (3) : shows a significant decrease in the mean fasting serum level of Apo CII from 71.41 ± 18.09 ug/ml (i.e. 7.14 mg/dl) to 54.31 ± 17.58 ug/dl) (i.e. 5.43 mg/dl) and a decrease in the mean fasting serum level of Apo CIII from 13.90 ± 6.11 ng/ml to 13.08 ± 7.52 ng/ml after cinnamon intake period.

Concerning both mean fasting serum apolipoprotein CII (Apo CII) and apolipoprotein CIII (Apo CIII) after cinnamon intake; Apo CII decreased significantly from 71.41 ± 18.09 ug/ml (i.e. 7.14 mg/dl) to 54.31 ± 17.58 ug/dl) (i.e. 5.43 mg/dl) with P 0.000 while Apo CIII decreased from 13.90 ± 6.11 ng/ml to 13.08 ± 7.52 ng/ml with P = 0.711 table (1) and figure (3).

DISCUSSION:

Atherosclerotic changes of the blood vessels of the body, start essentially by what is called endothelial dysfunction (ED). ED starts in an insidious manner years before organic pathological changes occur in the vessel wall; And decades before clinical symptoms start to appear. It may extend and affect several vascular beds of the body with varying extents and intensities (Steffel and Luscher, 2009).

In fact, the integrity of the arterial tree depends on its healthy lining endothelium. The healthy endothelial cells secrete a protective substance which is termed the "endothelium derived relaxing factor (EDRF)". This protective hormone is nitric oxide (NO) in nature. It exerts its anti-atherosclerotic effect through relaxing the vascular smooth muscle cells and preventing their proliferation, impeding leucocytes adhesion and migration into the arterial wall. It also prevents platelet adhesion and aggregation. In addition, it reduces adhesion molecule expression (Luscher, 1988). After the advent of oxidative stress theory, it has been proved that this pathophysiological state can negatively affect the healthy endothelial function. This results in reduced bioavailability of the protective EDRF either by its reduced production by the enzyme endothelial NO synthase, or more frequently due to its increased breakdown by reactive oxygen speies (ROS) production (Taddei et al., 2003; Luscher and Vanhoutte 2000). ROS production increases in the presence of atherosclerotic risk factors including diabetes mellitus, obesity, dyslipidemia, hypertension and smoking. Also, ROS are usually generated by and accompany bad dietary habits with high caloric diet with surplus in macronutrients including carbohydrates, proteins and fats. These result in high serum glucose (Mohanty et al., 2000), amino acids, lipids and free fatty acids (Mohanty et al., 2002).

Endothelial dysfunction is not only the starting step of atherosclerosis, but it also propagates the atherosclerotic disease process silently to a point where it may be irreversible and the endothelium acquires a pro atherogenic state. In fact oxidative stress excites a chronic systemic inflammatory state which implicates the endothelial cells (Stirban et al., 2006). Here organic structural changes in the vessel wall start to appear. Small size low density lipoprotein (LDL) particles in blood invade the endothelium and percolate in the intima. These become oxidized by ROS and create a risk for the vessel (Leitinger, 2003). The excited inflammatory process is accompanied by invasion of the vessel wall by macrophages which engulf the oxidized LDL particles and change into foam cells which reside insitu forming fatty streaks, fibrofatty changes and atheromotous plaques (Stary et al., 1995; Stary et al., 1994; Glagov et al., 1987).

In the present work we tried to find out the effect of cinnamon powder ingestion on certain steps in the pathogenesis of atherosclerosis, namely oxidative stress, types of cholesterol and Apo lipoproteins CII and CIII as inflammatory markers.

In the process of oxidative stress, we estimated serum malondialdehyde (MDA) as a universally accepted biomarker for its assessment (Zorawar et al., 2014). At the same time, we estimated paraoxonase-1 (PON-1) as a protective parameter against lipid peroxidation (Litvinov et al., 2012). In this study MDA dropped markedly after the period of cinnamon ingestion, meanwhile PON-1 significantly increased after the same period.

PON-1 is an enzyme of the family paraoxonase enzymes (PON-1, 2, 3). PON-1 is found in the liver, other body tissues and in plasma; usually associated with high density lipoprotein (HDL). This hydrolytic enzyme has been proved to be protective against atherosclerosis (Camps et al., 2012). In fact, it acts against oxidative stress and systemic (metabolic) inflammation. It seems to act in concert with other antioxidant enzymes like superoxide dismutase (SOD) (Sozmen et al., 2001). The cooperation with other antioxidant enzymes besides being effective, it preserves their antioxidant efficacy (Rosenblat et al., 2006). It also reduces oxidation of LDL particles which are taken by macrophages to form foam cells. These latter when accumulate result in atheromatous plaque formation (Aviram and Rosenblat, 2004). Oxidized LDL particles, also excite the vascular endothelial cells to secrete monocyte chemo attractant protein-1 (MCP-1) thus enhancing atherosclerosis progression. PON-1 inhibits MCP-1 production by the vascular endothelium (Macknees et al., 2004). PON-1

helps HDL to bind to macrophages and at the same time enhances the efflux of cholesterol from these cells (Rosenblat et al., 2005; Navab et al., 2001).

In the present work, we also studied the effect of cinnamon on blood cholesterol level which plays a pivotal role in the process of atherogenesis and its propagation (Lu et al., 2003). Cinnamon ingestion decreased total cholesterol, LDL and increased HDL. Although the period of cinnamon ingestion was short and the obtained values are not statistically significant, yet the pattern of change is impressive. The drop in total cholesterol, the bad cholesterol (LDL) and the rise in good cholesterol (HDL) point to an anti-atherogenic pattern (Brunzell et al., 2008).

Again, in the present work we estimated apolipoprotein CII (Apo CII) and apolipoprotein CIII (Apo CIII) as inflammatory markers. Apo CII is an integral component of chylomicrons and the blood lipoproteins: very low density lipoproteins (VLDL), LDL and HDL. The normal serum level of apo CII is in the range of 3-5 mg/dl (Malati and Mahesh, 2009). In this range, it acts as an activator of the lipoprotein lipase enzyme (LPL). When Apo CII is present in concentrations around 4 mg/dl, it reaches its optimum activity. However, when Apo CII level is low or present in excess, its LPL activating action is reduced. This is accompanied by HDL particles rich in triglycerides together with HDL altered distribution and defective in action. All these are atherogenic (Kei et al., 2012). In the present study, cinnamon ingestion significantly reduced Apo CII level from 7.14 mg/dl to 5.43 mg/dl which means improving the LPL activity.

On the other hand, in the present study Apo CIII was also estimated. This is a small protein moiety which is attached to the surface of the different lipoproteins in the body and increases their atherogenecity. It inhibits the clearance of these atherogenic plasma lipoproteins (VLDL and LDL) by the liver (Zheng et al., 2010).

This pro-inflammatory protein which is attached to the surface of VLDL and LDL may extend to some subclasses of HDL imparting its atherogenic effect on it (Talayero et al., 2014). Apo CIII is a LPL inhibitor which inhibits the lipolysis of triglycerides content in HDL impairing its capability for transporting cholesterol and its efflux from tissues engorged with cholestryl esters such as the vascular walls (Ansell et al., 2003). HDL containing Apo CIII, also do not prevent the pro-inflammatory monocytes from adherence to endothelial cells in humans, which adds to the atherogenic inflammatory process in the vessel wall (Kawakami et al., 2006). In the present work cinnamon ingestion substantially reduced Apo CIII plasma level in the patients examined.

CONCLUSION

In conclusion and in view of the obtained results, cinnamon can be used as a supplementary agent in the management of atherosclerotic risk conditions such as obesity, type 2 diabetes mellitus, metabolic syndrome, hypertension and dyslipidemia. Cinnamon tackled several important facets in the process of atherogenesis. It improved the oxidative stress, the lipid profile and the inflammatory state. In our opinion, this study of cinnamon on the above parameters deserves to be extended for a longer duration and on a wider scale to obtain more defined dosage.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEGEMENT

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AUTHOR CONTRIBUTIONS

MWG, WGN performed the patient selection, clinical aspect, study design, data analysis, writing and meticulous revision of manuscript. DFH, ERY, NMA peformed the biochemical and laboratory part. MEE gave valuable insights regarding this work. All authors read and approved the final version.

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