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Research Article

# Effect of Cinnamon Supplementation on Oxidative Stress, Inflammation and Insulin Resistance in Patients with Type 2 Diabetes Mellitus

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**ABSTRACT**
We performed a randomized, double blind, placebo controlled trial to investigate the effect of cinnamon supplementation on malondialdehyde (MDA), total antioxidant capacity (TAC), high sensitive-C-reactive protein (hs-CRP), insulin sensitivity and insulin resistance in 49 patients with type 2 diabetes mellitus (T2DM) and 57 T2DM patients were the placebo group. All participants received either cinnamon or placebo identical capsule daily for 60 days study period. At the end of the study, the median of MDA, hs-CRP levels and insulin resistance were significantly decreased ($p$<0.005) while TAC and insulin sensitivity were significantly increased ($p$<0.005) with in the cinnamon supplementation group. In placebo group, we found that MDA and hs-CRP levels were significantly increased ($p$<0.05) and TAC was significantly decreased ($p$<0.05) while insulin resistance, insulin sensitivity and insulin levels were not significantly different. Supplementation with cinnamon significantly reduced oxidative stress, insulin resistance, inflammation while increased TAC and insulin sensitivity in T2DM patients. Cinnamon supplementation could be considered as an additional dietary supplement option to prevent and regulate underlying diabetic complications.

**Key words:** Type 2 diabetes mellitus, cinnamon, oxidative stress, hs-CRP, insulin resistance

## INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a metabolic disorder with multiple etiology and is one of the leading causes of morbidity and mortality worldwide[1], which is characterized by hyperinsulinaemia, insulin resistance, β-cell dysfunction and subsequent β-cell failure[2]. T2DM is associated with both microvascular (such as retinopathy, nephropathy, and neuropathy) and macrovascular (cardiovascular diseases; CVD) complications[3,4]. The incidence of cardiovascular diseases is increased two to four fold in people with T2DM[5]. T2DM leads to cardiovascular damage through different mechanisms such as activation of protein kinase C, polyol and hexosamine pathways and advanced glycation end products production. All of these pathways, in association to hyperglycemia-induced mitochondrial dysfunction and endoplasmic reticulum stress, promote reactive oxygen species (ROS) accumulations that promote cellular damage and contribute to the diabetic complications development and progression[6]. Hyperglycemia-induced oxidative stress induces endothelial dysfunction that plays a central role in the pathogenesis of micro- and macro-vascular diseases[6].

Although the causes of T2DM and cardiovascular diseases are multifactorial, diet definitely plays a role in the incidence and severity of these diseases. The conventional pharmacological treatments for T2DM have a number of limitations, such as adverse effects and high rates of secondary failure. However, medicinal herbs are expected to have a similar efficacy without the side effects associated with conventional drug treatment. Recent studies demonstrate that plants are important for the prevention and control of T2DM. Polyphenols are the end products of the flavonoid biosynthesis in plants and are used by plants for the protection against predators[7]. Plant polyphenols are also widely present in human food stuff [8] and are important for human health[8], including prevention and/or treatment oxidative stress and insulin resistance[9]. Hence studies have frequently focused on dietary components beneficial in prevention and treatment. In general, we used *Cinnamomum* genus as a medicinal herb; both Ceylon cinnamon (*Cinnamomum zeylanicum*) and Chinese Cassia cinnamon (*Cinnamomum aromaticum*) are the most widely available varieties[10]. The main active ingredient of cinnamon is considered to be doubly linked A type polyphenols, which are A type doubly linked

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Table 1: Baseline characteristics of treatment and placebo type 2 diabetes groups

| Baseline characteristics | Treatment group (n = 49) | Placebo group (n =57) |
|---|---|---|
| Age (years) | 57.5 ± 1.1 | 56.9 ± 1.2 |
| Sex | | |
| Males | 16 (32.7%) | 16 (28.1%) |
| Females | 33 (67.3%) | 41 (71.9%) |
| Time since diagnosis of type 2 diabetes (years) | 9.04± 4.76 | 8.14±2.75 |
| Number of capsules remaining (capsule count after 12 weeks) | 1 | 2 |
| Blood pressure or cholesterol-lowering medication | | |
| Anti-hypertensive only | 18 (36.7%) | 19 (33.3%) |
| Statins only | 9 (18.4%) | 12 (21.1%) |
| Both anti-hypertensive and statins | 22 (44.9%) | 26 (45.6) |
| Glucose-lowering medication | | |
| Metformin | 24 (49%) | 25 (43.9%) |
| Sulphonylureas | 5 (10.2%) | 7 (12.3%) |
| Both metformin and sulphonylureas | 20 (40.8%) | 25 (43.9%) |
| Diagnosed medical conditions of hypertension or dyslipidemia | | |
| Hypertension | 24 (48.9%) | 33 (57.9%) |
| Dyslipidaemia | 31(63.3%) | 33 (57.9%) |
| Both hypertension and dyslipidaemia | 16 (51.6%) | 22 (66.7%) |

Data presented as mean ±sd and n (%).

*P*> 0.05 (v2-test) shows that there were no statistically significant difference observed between the cinnamon and placebo groups in termsof age, sex, time since diagnosis of diabetes, blood pressure and cholesterol-lowering medications, glucose-lowering medication, diagnosed medical conditions of hypertension and dyslipidaemia,

Table 2: Baseline characteristics of treatment and placebo groups

| | Treatment group (n=49) | Placebo group (n=57) | *P*-value |
|---|---|---|---|
| Age (years) | 57.2 ±1.1 | 56.9±1.2 | 0.939 |
| Sex | | | |
| Male | 16 (32.7%) | 16 (28.1%) | - |
| Female | 33 (67.3%) | 41 (71.9%) | - |
| BMI (kg/m2) | 24.7 (22.1-27.4) | 24.7 (22.5-27.4) | 0.259 |
| WC (cm) | 90.0 (84.5-96.5) | 89.0 (85.0-96.0) | 0.055 |
| Systolic BP(mmHg) | 134.5 (126.8-144.0) | 135.0 (127.0-142.0) | 0.652 |
| Diastolic BP(mmHg) | 83.5 (79.0-91.3) | 80.0 (73.5-90.0) | 0.792 |
| Baseline glucose (mmol/l) | 8.53 (7.26-10.56) | 7.59 (6.38-9.19) | 0.887 |
| Insulin (pmol/L) | 34.80 (24.60-65.7) | 28.80 (22.20-46.80) | 0.073 |
| HOMA-IR | 2.11 (1.37-3.64) | 1.63 (1.14-3.04) | 0.063 |
| HOMA%β | 27.89 (15.80-54.17) | 23.46 (15.48-38.80) | 0.372 |
| QUICKI | 0.341 (0.315-0.364) | 0.354 (0.323-0.375) | 0.064 |
| MDA(µmol/L) | 3.65 (3.01-5.76) | 3.54 (2.99-5.72) | 0.653 |
| TAC (µmolTroloxEquiv/L) | 4.516 (3.557-6.164) | 3.700 (3.150-5.910) | 0.051 |
| hs-CRP (g/L) | 0.025 (0.011-0.058) | 0.018 (0.009-0.034) | 0.153 |

procyanidin oligomers of the catechins and/or epicatechins. These polyphenolic polymers found in cinnamon may function as antioxidants[10], potentiate insulin action, and may be beneficial in the control of glucose intolerance and diabetes[9] as well as reducing cardiovascular disease and boosting cognitive function[11]. Cinnamaldehyde, one of major cinnamon contents, has been found to reduce lipopolysaccharide (LPS)-induced nuclear factor kappaB (NF-kB) transcriptional activity through the inhibition of DNA binding activity in macrophages[12]. In addition, cinnamaldehyde was found to reduce interleukin-1b(IL-1b)-induced cyclooxygenase-2 activity in endothelial cells and to exert several biological effects such as anti-angiogenic activity and immunomodulating activity[13]. Cinnamon also produces protective action against lipid and protein oxidation on membrane organization using the ability of cinnamon phenolics to scavenge ROS[14].

Given these findings, we hypothesized that cinnamon herb acted with insulin-like biological and antioxidant activities[15] and could improve oxidative stress, total antioxidant capacity, inflammatory insulin sensitivity and insulin resistance in patients with T2DM. Therefore, our present study was designed to investigate the effects of a sixty days supplementation with cinnamon capsule on insulin resistance, insulin sensitivity, insulin levels, oxidative stress, total antioxidant capacity and highly sensitive C-reactive protein (hs-CRP), an inflammatory marker in T2DM subjects.

Table 3: Effect of cinnamon on glucose, insulin, HOMA-IR, HOMA%β, QUICKI, MDA, TAC and hs-CRP in T2DM patients

| | Baseline | Final supplement | Difference | *P*-value |
|---|---|---|---|---|
| Glucose (mmol/l) | 8.53 (7.26-10.56) | 7.32 (6.52-9.85) | 0.55 (0.47-1.82) | 0.026 |
| Insulin (pmol/L) | 34.80 (24.60-65.7) | 26.40 (19.50-42.00) | 10.20(1.20-20.40) | <0.001 |
| HOMA-IR | 2.11 (1.37-3.64) | 1.95 (1.18-2.63) | 0.40 (-0.22-1.24) | 0.003 |
| HOMA%β | 27.89 (15.80-54.17) | 20.42 (12.39-28.55) | 8.95 (0.98-24.06)) | <0.001 |
| QUICKI | 0.341 (0.315-0.364) | 0.345 (0.330-0.372) | -0.011 (-0.027-0.007) | 0.006 |
| MDA(µmol/L) | 3.65 (3.01-5.76) | 3.22 (2.68-3.62) | 0.89 (0.08-2.11) | <0.001 |
| TAC (µmolTroloxEquiv/L) | 4.516 (3.557-6.164) | 4.880 (4.015-6.245) | -0.24 (-0.54- -0.05) | <0.001 |
| hs-CRP (g/L) | 0.025 (0.011-0.058) | 0.014 (0.009-0.026) | 0.008 (-0.001-0.037) | <0.001 |

## MATERIALS AND METHODS

Subjects: Our study was a randomized, double blind, placebo controlled trial in T2DM patients. These patients were randomly selected from a volunteer list who previously had attended the Diabetes Care Clinic activities of the Ladyao Hospital, Nakornsawan Province (December 2012-December 2013). The randomization of these patients was done by using a table of random numbers with block of four to receive cinnamon or placebo. The treatment code was concealed by placing the patient's assignments in sequence in sealed opaque envelopes that were drawn in ascending consecutive order. The codes were kept strictly confidential for blinding the researchers and subjects those were broken at the end of the study. These patients have been diagnosed or received medications as T2DM over 5 years, aged ≥40 years old, no acute cardiovascular or neurologic event in the prior 6 months, no history of active tobacco smoking and no oral intake of vitamin supplements in the last 4 weeks and the medical treatment for diabetes had to be stable for the last 3 months as the inclusion criteria. The exclusion criteria were overt cardiovascular, neuromuscular, arthritic, pulmonary or other debilitating diseases and those who currently smoked or had poor glycemic control or were on insulin treatment. Medications were not altered in either group during the study period. The duration of diabetes was similar in both experimental and control groups: 9.04± 4.76 years for the cinnamon groups and 8.14±2.75 years for the placebo group.

The identical-looking capsules of Cinnamon (*Cinnamomum cassia*) capsules and placebo capsules were purchased from the Government Pharmaceutical Organization, Thailand. After baseline assessment for eligibility, all patients were requested to take one cinnamon capsules (500 mg) or placebo capsules after meal three times a day (as suggested in the leaflet), everyday for a total of 60 days. Patients were requested to take their conventional medication and record their randomized tablets in each day. One 24 h recall was conducted for each subject and especially elderly patients. Patients were advised to control their meals with low carbohydrate and low fat same as the physician suggestion. All patients were requested to return the day after completing their study period to assess the effect of the supplementation. All subjects provided written informed consent before participating and providing blood sample for their health check in this study. The study protocol was approved by the Ethics Committee of the Naresuan University (55-03-01-0020).

*Anthropometric and blood pressure measurement*

Height, weight and blood pressure (BP) were measured and body mass index (BMI) was calculated. Waist circumference (WC) was measured at the midpoint between the both of rib cage and the top of lateral border of iliac crest during minimal respiration. BP was measured after the participants were seated and rested for 5 minutes as the mean value of at least two measurements of these participants on the same day with a Terumo digital blood pressure monitor (ES-P110).

*Blood sample collection and biochemical determination*

Venous blood samples were collected without stasis after a 12 hour fast and a 30 minutes rest in a supine position. Blood specimens were processed and assayed at the clinical laboratory of Ladyao Hospital, Nakornsawan.

*Insulin assay*

Fasting insulin levels were measured based on micro-particle enzyme immunoassay (MEIA) technology using Abbott reagents with Axsym system (Abbott laboratories, Illinois, USA). All participants underwent evaluation of all insulin markers by using the Homeostasis model assessment (HOMA)-formula[16]. HOMA-IR was defined using the following formula: fasting glucose (mmol/l) x fasting insulin (µU/ml)/22.5, β-Cell function (HOMA% β) = [20*insulin (µU/ml)]/[glucose(mmol/l)-3.5)] [17]. Quantitative Insulin Sensitivity Check Index (QUICKI) = 1/[LOG insulin (µU/ml) + LOG glucose (mg/dl)] [18].

*Malondialdehyde (MDA) assay*

The method is based on the formation of red (pink) chromophore following the reaction of thiobarbituric acid with MDA and the other breakdown products of peroxidized lipids called thiobarbituric acid reactive substance (TBARS). One molecule of MDA reacts with 2 molecules of TBA to yield a pink pigment with maximum

Table 4: Effect of placebo supplementation on glucose, insulin, HOMA-IR, HOMA%β, QUICKI, MDA, TAC and hs-CRP in T2DM patients

| | Baseline | Finalsupplement | Difference | *P*-value |
|---|---|---|---|---|
| Glucose (mmol/l) | 7.59 (6.38-9.19) | 8.03 (6.38-10.51) | -0.50 (-1.60-0.52) | 0.058 |
| Insulin (pmol/L) | 28.80 (22.20-46.80) | 33.60 (21.60-51.00) | -1.20 (-12.30-8.70) | 0.400 |
| HOMA-IR | 1.63 (1.14-3.04) | 2.09 (1.12-3.15) | -0.20 (-0.99-0.43) | 0.251 |
| HOMA%β | 23.46 (15.48-38.80) | 25.44 (12.91-48.19) | -0.45 (-13.03-10.14) | 0.688 |
| QUICKI | 0.354 (0.323-0.375) | 0.341 (0.321-0.376) | 0.006 (-0.014-0.023) | 0.304 |
| MDA(µmol/L) | 3.54 (2.99-5.72) | 4.42 (3.14-5.94) | -0.29 (-1.03-0.00) | <0.001 |
| TAC (µmolTroloxEquiv/L) | 3.700 (3.150-4.910) | 3.250 (2.040-4.070) | 0.51 (0.34-1.18) | <0.001 |
| hs-CRP (g/L) | 0.018 (0.009-0.034) | 0.020 (0.013-0.034) | -0.003 (-0.009-0.003) | 0.045 |

Table 5: Comparison of the changing in concentrations of each variable of the Cinnamon supplement with the placebo group after the study session for both T2DM groups

| | Conc. Change in Cinnamon supplement | Conc. Change in placebo group | *P*-value |
|---|---|---|---|
| Glucose (mmol/l) | 0.55 (0.47-1.82) | -0.50 (-1.60-0.52) | 0.001 |
| Insulin (pmol/L) | 10.20(1.20-20.40) | -1.20 (-12.30-8.70) | <0.001 |
| HOMA-IR | 0.40 (-0.22-1.24) | -0.20 (-0.99-0.43) | 0.002 |
| HOMA%β | 8.95 (0.98-24.06)) | -0.45 (-13.03-10.14) | 0.001 |
| QUICKI | -0.011 (-0.027-0.007) | 0.006 (-0.014-0.023) | 0.006 |
| MDA(µmol/L) | 0.89 (0.08-2.11) | -0.29 (-1.03-0.00) | <0.001 |
| TAC (µmolTroloxEquiv/L) | -0.24 (-0.54- -0.05) | 0.51 (0.34-1.18) | <0.001 |
| hs-CRP (g/L) | 0.008 (-0.001-0.037) | -0.003 (-0.009-0.003) | <0.001 |

absorption at 532 nm. This was measured by spectrophotometry using 1,1,3,3-tetraethoxypropane (TEP) as standard as described previously [19]. The final results were expressed as µmol of MDA formed per liters of serum. Intra-assay and inter-assay imprecision were 3.24% and 5.78%, respectively. The normal range of MDA was <3.5µmol/L.

*Total antioxidant capacity (TAC) assay*

The method is based on formation of the $ABTS^{\bullet+}$cation [2,2'-azinobis (3-ethylbenzothiazoline-6-sulfonic acid)] and its scavenging by antioxidant sample constituents (serum) measured by spectrophotometry at 600 nm (decay of green/blue color absorption is inversely associated with antioxidant sample content and the control antioxidant is Trolox, a hydrophilic vitamin E analog)[20].

*High sensitivity (hs)-CRPassays*

hs-CRP concentrations were determined using latex-enhanced immunoneplelometric assay on the Hitachi 912 auto-analyzer (Roche Diagnostic, Switzerland) that has been standardized against the World Health Organization reference. The normal range of hs-CRP was <0.03 g/L (<3.0 mg/L). Standard curves were constructed for determination of each analyte concentration according to the manufacturers' instructions.

*Statistical analysis*

Categorical data are presented as percentages, and continuous data are presented as mean± standard deviation (SD) or median and interquartile range for non-normally distributed data, and tested by using Kolmogorov-Smirnov Test. The differences of these clinical data within the same subjects were analyzed by Friedman Test with repeated by Wilcoxon signed ranks tests (2-tailed non-parametric tests) were used to assess the differences between the baseline and 60 days period after receiving supplements in both groups (intragroup) and the Mann Whitney U-test was applied for detection of the differences of intergroup (both groups) differences. *P*-values less than 0.05 were considered statistically significant. All analysis was performed using the SPSS computer program version 13.0 (SPSS, Chicago, IL).

## RESULTS

All baseline characteristics of the present study are list in Table 1. Forty nine subjects of the cinnamon supplementation group were carried out the 60-days period

of continuous supplement without any adverse events. During the intervention period, three participants dropped out of the supplement group, and two others were later excluded from our study because they stopped taking antidiabetic medication during the cinnamon intervention period. Fifty seven of placebo group (95%) participated until the end of study session, while three of placebo group dropped out from the study because they moved to work with their families in other provinces.

Our data demonstrated significantly differences in each groups ($p$<0.05) by using Friedman Test. We further comparison the baseline characteristics of cinnamon and placebo groups. Both T2DM groups are not significantly different as shown in Table 2. All clinical characteristics at the baseline and the end of the study period of each supplementation and placebo groups were analyzed by using Wilcoxon signed ranks tests as shown in Table 3, 4. In cinnamon supplementation group demonstrated that MDA, hs-CRP, glucose, insulin levels, HOMA-IR and HOMA%β were significantly decreased ($p$<0.05) while TAC and QUICKI were significantly increased ($p$<0.05). Our study demonstrated no weight loss effect on cinnamon supplementation. In the placebo group, we found that MDA and hs-CRP levels were significantly increased ($p$<0.05) and TAC was significantly decreased ($p$<0.05) at the end of the study period while glucose, HOMA-IR, HOMA%β, QUICKI and insulin levels were not significantly different but trend to increase in these markers. We also compared the concentration change of each variable in both groups. We found that glucose, insulin, HOMA-IR, HOMA-%β, MDA and hs-CRP were significantly decreased while QUICKI and TAC were significantly increased in cinnamon supplementation group more than placebo group as shown in Table 5.

## DISCUSSION

Our study demonstrated the health benefit by reduction of glucose, MDA, hs-CRP, insulin levels, insulin resistance (HOMA-IR), β-cell function (HOMA%β), and increasing insulin sensitivity (QUICKI) and TAC levels in the cinnamon supplementation group. Oxidative stress generation is proposed as the common persistent pathogenic factor mediating the appearance of insulin resistance while producing the increased cardiovascular risk by favoring atherosclerotic complications[4]. Evidence suggests that over-nutrition, insulin resistance, intolerance glucose tolerance test, diabetes, and CVD share in the presence of an increased oxidative stress[21]. Previous studies have suggested that T2DM is a disease in which ROS are involved in the pathogenesis of complications [19]. Oxidative stress has been demonstrated association with inflammation and insulin resistance[4, 22]. Oxidative damage leads to an inappropriate activation of the transcription factor NF-κB and subsequently to an over expression of inflammatory proteins[23]. Chronic subclinical inflammation, hs-CRP is a component of the insulin resistance, metabolic syndrome and all features of cardiovascular risk factors, including dyslipidaemia, endothelial dysfunction, hypertension, obesity and T2DM[24]. Reduction of oxidative stress and increased TAC activity demonstrate beneficial effect on insulin levels, insulin resistance, insulin sensitivity, antioxidant property[25, 26] and inhibit NF-κB activation[23] in cinnamon supplementation.

The main active ingredient of cinnamon is considered to be doubly linked A type polyphenols, which are A type doubly linked procyanidin oligomers of the catechins and/or epicatechins. These polyphenolic polymers found in cinnamon may function as antioxidants, potentiate insulin action, and may be beneficial in the control of glucose intolerance and diabetes[9]. As in the previous study, cinnamon is claimed to be a natural insulin sensitizer[25]. The insulin-sensitizing effect of cinnamon has been established in-vitro cell line studies with adipocytes[25,27] as well as in-vivo animal studies[16]. Methylhydroxychalcone polymer (MHCP) is also the one of bioactive compound isolated from cinnamon which acts as a mimetic of insulin[27] to increase glucose uptake in cells. Gruenwald et al. also showed that nutritional intakes of cinnamon improve insulin sensitivity and lead to beneficial antioxidant effects[12]. In particular, most anti-diabetic agents have both insulin-sensitizing and anti-inflammatory activities, both of which properties might be expected to oppose atherosclerosis and so reduce the risk of CVD. Hartel et al. found that antioxidants inhibited the LPS-induced IL-6 and TNF-α production, as well as IL-2 production after phorbol 12-myristate 13-acetate, ionomycin stimulation[28]. The cinnamon antioxidant reduced chronic inflammation, hs-CRP, may be mediated by effects on upstream cytokines, in particularly of IL-1, TNF-α, and IL-6, which are the main inducers of this acute phase response[29]. Thus, cinnamon can reduce a variety of oxidant species. These may cause the reduction of insulin secretion, insulin resistance, chronic inflammation and increasing insulin sensitivity as in our present study. These processes may also cause the reduction of dyslipidemia in the circulation following improved insulin secretion, β-cell function, insulin sensitivity and insulin resistance. The limitation of our study is that we did not measure the polyphenolic polymers and flavonoids contents in the blood circulation of the individual participants.

There are many conflict data of the effects of cinnamon on glycemic and/or insulin sensitivity and lipid profiles. Blevins et al. demonstrated the reversed effect of increased plasma glucose levels and no significant change in HbA1c after 3 months consumption of cinnamon cassia 1 to 1.2 g/d versus placebo. However, this trial was published only as a research brief, so many of the study characteristics were unclear[30]. Vanschoonbeek et al demonstrated that cinnamon supplementation (1.5 g/d) did not improve oral glucose tolerance, insulin sensitivity, lipid profile and hemoglobin A1c levels after 30 days supplementation of postmenopausal women with type 2 diabetes[31]. Altschuler et al. also demonstrated no beneficial effects of cinnamon in adolescents with type 1diabetes[32].

## CONCLUSION

According to our present study, cinnamon could be considered as an additional dietary supplement option to

prevent and regulate underling diabetic complications along with conventional medications to treat T2DM.

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**DECLARATION OF INTEREST:** none

**REFERENCES**

1. Goyal, B.R., Mehta, A.A., Diabetic cardiomyopathy: pathophysiological mechanisms and cardiac dysfunction. Hum.Exp.Toxicol. 2013.32, 571 -590.
2. Stumvoll, M., Goldstein,B.J., van Haeften, TW., Type 2 diabetes: principles of pathogenesis and therapy. Lancet. 2005.365, 1333–1346.
3. Arora, M.K., Singh,U.K., Molecular mechanisms in the pathogenesis of diabetic nephropathy: An update. Vascul. Pharmacol. 2013. 58, 259-271.
4. Rahman, S., Rahman, T., Ismail,A.A., Rashid, A.R., Diabetes-associated macrovasculopathy: pathophysiology and pathogenesis. Diabetes. Obes. Metab. 2007. 9, 767–780.
5. Raza, A., Movahed, A., Current concepts of cardiovascular diseases in diabetes mellitus. Int. J.Cardiol.2003.89, 123–134.
6. Fiorentino, T.V., Prioletta, A., Zuo, P., Folli, F., Hyperglycemia-induced oxidative stress and its role in diabetes mellitus related cardiovascular diseases.Curr. Pharm. Des. 2013.19, 5695-5703.
7. Dixon, R.A., Xie, D.Y., Sharma, S.B., Proanthocyanidins-a final frontier in flavonoid research? New. Phytol. 2005.165, 9-28.
8. Prior,R.L.,Gu, L., Occurrence and biological significance of proanthocyanidins in the American diet. Phytochemistry.2005.66, 2264-2280.
9. Dhuley, J.N., Anti-oxidant effects of cinnamon (*Cinnamomum verum*) bark and greater cardamom (*Amomum subulatum*) seeds in rats fed high fat diet. Indian J. Exp. Biol. 1999.37, 238-242.
10. Jayaprakasha, G., Jagan Mohan Rao, L., Chemistry, biogenesis, and biological activities of *Cinnamomum zeylanicum*. Crit. Rev. Food Sci. Nutr. 2011.51, 547–562.
11. Gruenwald, J., Freder, J., Armbruester, N., Cinnamon and health. Crit. Rev. Food. Sci. Nutr. 2010.50, 822–834.
12. Reddy, A.M., Seo, J.H., Ryu, S.Y., Kim, Y.S., Kim, Y.S., Min, K.R., Kim, Y., Cinnamaldehyde and 2-methoxycinnamaldehyde as NF-kappa B inhibitors from *Cinnamomum cassia*. Planta. Med. 2004.70, 823–827.
13. Guo,J.Y.,Huo, H.R., Zhao, B.S., Liu, H.B., Li, L.F., Ma, Y.Y., et al., Cinnamaldehyde reduces IL-1beta-induced cyclooxygenase-2 activity in rat cerebral microvascular endothelial cells. Eur. J. Pharmacol. 2006.537, 174–180.
14. Moselhy, S.S., Ali, H.K.H., Hepatoprotective effect of cinnamon extracts against carbon tetrachloride induced oxidative stress and liver injury in rats. Biol. Res. 2009.42, 93–98.
15. Qin, B., Nagasaki, M., Ren, M., Bajotto, G., Oshida, Y., Sato, Y., Cinnamon extract (traditional herb) potentiates in vivo insulin regulated glucose utilization via enhancing insulin signaling in rats. Diabetes. Res. Clin. Pract. 2003.62, 139–148.
16. Matthews, D.R., Hosker, J.P., Rudenski, A.S., Naylor, B.A., Treacher, D.F., Turner, R.C., Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia.1985.28, 412-419.
17. Haffner, S.M., Kennedy, E., Gonzalez, C., Stern, M.P., Miettinen, H., A prospective analysis of the HOMA model. The Mexico City Diabetes Study. Diabetes Care. 1996. 19, 1138-1141.
18. Duncan, M.H., Singh, B.M., Wise, P.H., Carter, G., Alaghband-Zadeh, J., A simple measure of insulin resistance. Lancet. 1995. 346, 120-121.
19. Tangvarasittichai, S., Poonsub, P., Tangvarasittichai, O., Sirigulsatien, V., Serum levels of malondialdehyde in type 2 diabetes mellitus Thai subjects. Siriraj Med. J. 2009.61, 20-23.
20. Miller, N.J., Rice-Evans, C., Davies, M.J., Gopinathan, V., Milner, A., A novel method for measuring antioxidant capacity and its application to monitoring the antioxidant status in premature neonates. Clin.Sci. (Lond). 1993.84, 407-412.
21. Griendling, K.K., FitzGerald, G.A., Oxidative stress and cardiovascular injury: Part I: basic mechanisms and in vivo monitoring of ROS. Circulation. 2003.108, 1912–1916.
22. Block, G., Dietrich, M.,Norkus, E.P., Morrow, J.D., Hudes, M., Caan, B., Packer, L., Factors associated with oxidative stress in human populations. Am. J. Epidemiol. 2002. 156, 274–285.
23. Kwon, H.K., Hwang, J.S., So, J.S., Lee, C.G., Sahoo, A., Ryu, J.H., et al., Cinnamon extract induces tumor cell death through inhibition of NF-kappaB and AP1. BMC. Cancer. 2010. 10, 392–401.
24. deFerranti, S.D., Rifai, N., C-reactive protein: a nontraditional serum marker of cardiovascular risk. Cardiovasc. Pathol. 2007. 16, 14–21.
25. Qin, B., Panickar, K.S., Anderson, R.A., Cinnamon: Potential Role in the Prevention of Insulin Resistance, Metabolic Syndrome, and Type 2 Diabetes. J. Diabetes. Sci. Technol. 2010. 4, 685 -693.
26. Anderson, R.A., Chromium and polyphenols from cinnamon improve insulin sensitivity. Proc. Nutr. Soc. 2008. 67, 48-53.
27. Jarvill-Taylor, K.J., Anderson, R.A., Graves, D.J., A hydroxychalcone derived from cinnamon functions as a mimetic for insulin in 3T3–L1 adipocytes. J. Am. Coll. Nutr. 2001. 20, 327–336.
28. Hartel, C., Strunk, T., Bucsky, P., Schultz, C., Effects of vitamin C on intracytoplasmic cytokine production

in human whole blood monocytes and lymphocytes. Cytokine. 2004. 27,101–106.
29. Baumann, H., Goldie, J., The acute phase response. Immunol. Today. 1994.15, 74–80.
30. Blevins S.M, Leyva M.J, Brown J, Wright J, Scofield R.H, Aston CE.Effect of cinnamon on glucose and lipid levels in non insulin-dependent type 2 diabetes. Diabetes Care. 2007. 30, 2236-2237.
31. Vanschoonbeek K, Thomassen B.J, Senden J.M, Wodzig W.K, van Loon L.J. Cinnamon supplementation does not improve glycemic control in postmenopausal type 2 diabetes patients. J. Nutr. 2006.136, 977-980.
32. Altschuler J.A, Casella S.J, MacKenzie T.A, Curtis K.M. The effect of cinnamon on A1C among adolescents with type 1 diabetes.Diabetes.Care. 2007.30, 813-816.