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Original article

Cinnamon extract lowers glucose, insulin and cholesterol in people with elevated serum glucose

Richard A. Anderson [a, *], Zhiwei Zhan [b], Rencai Luo [c], Xiuhua Guo [d], Qingqing Guo [d], Jin Zhou [e], Jiang Kong [f], Paul A. Davis [g], Barbara J. Stoecker [h]

[a] PolyChrom Technology, LLC, Edgewater, MD 21037, USA
[b] The General Hospital of 2nd Artillery, Beijing, China
[c] Beijing CDC, Beijing, China
[d] Beijing Capital Medical University, Beijing, China
[e] Dalian Dakang Clinic, Dalian, China
[f] Beijing Tang-An Clinic, Beijing, China
[g] Department of Nutrition, University of Calif-Davis, Davis, CA, USA
[h] Oklahoma State University, USA

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ABSTRACT

Cinnamon (肉桂 ròu guì) has *in vitro* insulin potentiating activity, and proanthocyanidins from cinnamon prevent *in vitro* formation of advanced glycation end products. Some human studies were equivocal, but several have shown beneficial effects of cinnamon supplementation on circulating glucose, lipids, and/or insulin. This placebo-controlled double-blind trial tested the effects of a dried water extract of cinnamon (*Cinnamomum cassia*) on circulating glucose, lipids, insulin, and insulin resistance. Men and women from Beijing and Dalian, China, were invited to participate if they had fasting serum glucose >6.1 mmol/L or 2-h glucose >7.8 mmol/L. Participants, (173 were enrolled and 137 completed the study) were randomly assigned to receive either a spray-dried, water extract of cinnamon (CinSulin®), 250 mg/capsule, or a placebo, twice a day for two months. Mean ± SEM age of participants was 61.3 ± 0.8 years, BMI was 25.3 ± 0.3 and M/F ratio was 65/72. After 2 mo, fasting glucose decreased ($p < 0.001$) in the cinnamon extract-supplemented group (8.85 ± 0.36 to 8.19 ± 0.29 mmol/L) compared with the placebo group (8.57 ± 0.32 to 8.44 ± 0.34 mmol/L, $p = 0.45$). Glucose 2 h after a 75 g carbohydrate load, fasting insulin, and HOMA-IR also decreased with cinnamon extract compared with placebo. Total and LDL-cholesterol decreased with cinnamon extract and HDL-cholesterol decreased in both the cinnamon-extract and placebo groups. In conclusion, supplementation with 500 mg of water-extract of cinnamon for two months reduced fasting insulin, glucose, total cholesterol, and LDL cholesterol and enhanced insulin sensitivity of subjects with elevated blood glucose.

1. Introduction

Cinnamon (*Cinnamomum verum, Cinnamomum zeylanicum*; 錫蘭肉桂 xī lán ròu guì) and cassia (*Cinnamomum aromaticum*; 中國肉桂 zhōng guó ròu guì) have a long history of uses as flavoring agents, preservatives, and pharmacological agents.[1] In addition, in 2004, Khan et al[2] reported that subjects with type 2 diabetes given 1, 3 or 6 g of ground cinnamon per day for 40 days showed significant reductions in fasting serum glucose (18–29%), triglycerides (23–30%), LDL cholesterol (7–27%), and total cholesterol (12–26%) with no significant changes in the placebo group. Several follow-up human studies have also reported beneficial effects of cinnamon on people with varying degrees of glucose intolerance ranging from normal to type 2 diabetes.[3–13] Not all studies have reported beneficial effects of cinnamon or cinnamon extracts in human supplementation trials. However, three of four recent meta-analyses conclude that there are positive effects of supplemental cinnamon or cinnamon extract and that further studies are needed.[10,14–16]

* Corresponding author. Tel./fax: +1 410 798 0846.
E-mail address: PolyChrom.Anderson@gmail.com (R.A. Anderson).

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One region where further studies are needed is China with only a single positive study.[13] The present study used a spray-dried water-extract of cinnamon for supplementing adults with hyperglycemia in a placebo controlled double-blind two-month trial conducted in China. In China, it is estimated that there are 90 million people with diabetes and over 150 million people with prediabetes who are likely to become diabetic due to the current rapidly changing lifestyle in China.[17] (替代醫療 tì dài yī liáo) are urgently needed to control the hyperglycemia which precedes the escalating incidence of type 2 diabetes and the resulting exploding health care costs.

2. Research design and methods

2.1. Study participants

Men and women with fasting serum glucose >6.1 mmol/L or 2-h glucose >7.8 mmol/L from the clinic of the General Hospital of the 2nd Artillery, Beijing Tang-An Clinic and Dalian Dakang Clinic, in Beijing and Dalian, China, were invited to join this study. Exclusion factors were fasting glucose >20 mmol/L or 2-hr glucose >25 mmol/L, serum insulin <5 IU, taking insulin therapy, or serious complications such as cardiac/cerebral vascular diseases, or renal dysfunction. The study was approved by the human use committee of both hospitals and all participants gave informed consent.[18] Initially 173 persons were enrolled in the study, 89 in the placebo group and 84 in the treatment group. A total of 137 completed the study with 73 in the placebo group and 64 in the treatment group. No complications were reported in either the placebo or the treatment groups; the 36 subjects who did not complete the study were dropped because of a change in medication or missing a blood draw. Participants were asked to return their capsule bottles to allow study personnel to confirm study compliance.

2.2. Study design

Study participants were assigned to groups using a random number table in this double-blind placebo-controlled trial. The treatment group received a commercially available spray-dried water extract of cinnamon (肉桂 ròu guì) (CinSulin®) containing more than 4% type A procyanidin polyphenols,[19] in 250 mg capsules, twice a day. (This product does not contain added chromium or Vitamin D which is found in some commercial products using the same name). Type A procyanidin polyphenols are associated with insulin potentiating,[19–22] antioxidant[5,23] and anti-inflammatory activities.[24,25] The control group received placebo capsules which contained 250 mg of dark brown (baked) wheat flour and were very similar in appearance to the cinnamon extract.

2.3. Outcomes

In the present study, the by-group differences in fasting and in 2-hr serum glucose and in insulin resistance estimated as HOMA-IR were the primary outcome variables. Additional measurements included systolic and diastolic blood pressure, serum lipids, and fructosamine.

2.4. Anthropometry and clinical procedures

Height and weight were measured initially and weight was repeated at the end of the study. Subjects wore light clothing and removed their shoes for these measurements. Body mass index was calculated as weight (kg) divided by height (m^2). The Chinese Nutrition Society recommends BMI cutoffs of 28 for obesity and 24 for overweight.[26]

Blood pressure was measured after the participants had rested for 15 min and measurements were repeated two times. Postprandial glucose was obtained by measuring plasma glucose two hours after each participant consumed 100 g of white steamed bread (equivalent to 75 g of carbohydrate).

2.5. Biochemical analyses

Serum glucose and lipids were analyzed on a Hitachi 7071A clinical analyzer. Insulin was analyzed by radioimmunoassay and fructosamine with a kit from RANDOX Laboratories.

2.6. Quantitative glycemic measures

The homeostasis model assessment for insulin resistance (HOMA-IR) was used as a proxy measurement of insulin sensitivity. HOMA-IR was calculated as (fasting serum glucose × fasting serum insulin) divided by 22.5.[27]

2.7. Statistical analyses

Descriptive statistics were summarized as means and standard error of the mean using the SAS version 9.1 (SAS Institute, Cary, NC). Parameters that were heavily right skewed (fasting insulin, HOMA-IR, and triacylglycerols) were log transformed prior to statistical analyses. Treatment effects were analyzed using analysis of variance with repeated measures (PROC MIXED) with an autoregressive period 1 error structure. The simple effect of treatment given time (SLICE option in an LSMEANS statement) was used to identify significant changes from baseline with supplementation with cinnamon extract.

3. Results

3.1. Baseline characteristics of subjects

Mean ± SEM age of participants was 61.3 ± 0.8 y; 47% were men. Mean body mass index (BMI) was 25.3 ± 0.3 but 56% of the subjects had BMI between 24–28, which based on Chinese standards,[26] is classified as overweight; nearly 14% were classified as obese with BMI >28. Participants were hyperglycemic with baseline fasting glucose values of 8.70 ± 0.24 mmol/L (Table 1). Baseline parameters for the entire group for fasting insulin, postprandial glucose and insulin, lipids and blood pressure are also shown in Table 1.

Fasting insulin and HOMA-IR were significantly higher in the overweight and obese groups than in the normal weight group (Table 1). The insulin at 2 h after a glucose load was markedly and significantly higher in the obese group than in the groups with lower BMIs. Glucose and fructosamine values were not different for the three BMI groups. Diastolic blood pressure was significantly higher in the obese group. Total cholesterol and LDL-cholesterol were not significantly different by BMI, but HDL-cholesterol was significantly lower in the overweight and obese groups and triacyglycerols were higher in those two groups.

At baseline, homeostasis model assessment-estimated that insulin resistance (HOMA-IR) was significantly correlated with diastolic blood pressure ($r = 0.23$) postprandial glucose ($r = 0.45$), insulin ($r = 0.42$), triacylglycerols ($r = 0.29$), fructosamine ($r = 0.23$), and BMI ($r = 0.29$) and negatively correlated with HDL-cholesterol ($r = 0.37$).

Participants were assigned to placebo or treatment groups using a random number table. There were no significant differences at baseline in any parameters between the two groups (Table 2). After

Table 1
Baseline characteristics of subjects and classification by Chinese guidelines for body mass index (BMI) indicating normal, overweight, and obese.[a]

	All	BMI <24.0[b]	BMI ≥24.0–<28.0[c]	BMI ≥28.0[d]
Age, *years*	61.3 ± 0.8	59.0 ± 1.4	62.2 ± 1.0	62.4 ± 2.2
Fasting glucose, *mmol/L*	8.70 ± 0.24	8.99 ± 0.48	8.52 ± 0.28	8.82 ± 0.83
2-hr glucose, *mmol/L*	14.60 ± 0.42	14.61 ± 0.85	14.41 ± 0.51	15.37 ± 1.21
Fasting insulin, *mU/L*	22.9 ± 1.3	16.0 ± 1.3^{B}	24.4 ± 1.8^{A}	32.4 ± 4.2^{A}
2-hr insulin, *mU/L*	89.4 ± 3.9	76.2 ± 6.9^{B}	89.9 ± 5.0^{B}	114.8 ± 9.8^{A}
HOMA-IR	9.0 ± 0.6	6.6 ± 0.7^{B}	9.4 ± 0.8^{A}	13.2 ± 2.4^{A}
Fructosamine, *μmol/L*	343 ± 6	338 ± 11	344 ± 8	350 ± 13
Systolic blood pressure, *mm Hg*	125.3 ± 1.2	122.9 ± 2.6	125.1 ± 1.5	131.4 ± 3.4
Diastolic blood pressure, *mm Hg*	77.0 ± 0.7	75.4 ± 1.4^{B}	76.7 ± 0.8^{B}	81.3 ± 2.2^{A}
Total cholesterol, *mmol/L*	5.16 ± 0.09	5.19 ± 0.17	5.10 ± 0.11	5.35 ± 0.17
LDL cholesterol, *mmol/L*	3.46 ± 0.08	3.56 ± 0.15	3.38 ± 0.11	3.59 ± 0.20
HDL cholesterol, *mmol/L*	1.27 ± 0.03	1.41 ± 0.07^{A}	1.23 ± 0.03^{B}	1.16 ± 0.04^{B}
Triacylglycerols, *mmol/L*	2.12 ± 0.13	1.54 ± 0.15^{B}	2.32 ± 0.16^{A}	2.54 ± 0.59^{A}

[a] Mean ± SEM; Means (by BMI classification) in a row with superscripts (uppercase alphabets) are significantly different if they do not share a common letter. BMI classifications are based on recommendations from the Chinese Diabetes Association.
[b] $n = 37–41$ for glucose, insulin, HOMA-IR and blood pressure and 32 for lipids and fructosamine.
[c] $n = 77$ for glucose, insulin, HOMA-IR and blood pressure and 63 for lipids and fructosamine.
[d] $n = 17–19$ for glucose, insulin, HOMA-IR and blood pressure and 14–15 for lipids & fructosamine.

two months of supplementation with placebo or water-extract of cinnamon (肉桂 ròu guì), the only significant changes in the placebo group were an increase in triacylglyerols ($p < 0.0001$), an increase in systolic blood pressure ($p < 0.05$) and a decrease in HDL-cholesterol ($p < 0.005$). Cinnamon extract supplementation, lowered fasting serum glucose ($p < 0.001$) in the cinnamon-supplemented group, 8.85 ± 0.36 to 8.19 ± 0.29 mmol/L ($p < 0.005$), compared with 8.57 ± 0.32 to 8.44 ± 0.34 mmol/L in the placebo control group ($p = 0.45$). Serum glucose 2 h after a 75 g carbohydrate load also decreased significantly ($p < 0.0001$) in the cinnamon extract-supplemented group, 15.09 ± 0.57 to 13.3 ± 0.55 mmol/L, compared with non-significant differences in the placebo group, 14.18 ± 0.60 to 13.74 ± 0.58 mmol/L. Fasting insulin concentrations decreased significantly and postprandial insulin tended ($p < 0.06$) to be reduced by cinnamon extract supplementation. Insulin sensitivity, assessed by HOMA-IR, was significantly improved by cinnamon extract as were fructosamine concentrations.

Total cholesterol decreased with cinnamon extract supplementation as did LDL-cholesterol. HDL-cholesterol was decreased in both the placebo and cinnamon extract-supplemented groups and triacylglycerols increased in both groups (Table 2). Responses to cinnamon extract were independent of BMI.

4. Discussion

The incidence of type 2 diabetes (T2D) in China and worldwide is exploding and the associated morbidity, mortality and costs have energized the search for ways to reduce type 2 diabetes.[28] Impaired glucose tolerance (IGT) is a recognized intermediary condition between normal glucose regulation and T2DM and is associated with a substantially elevated risk of disease progression.[29] A recent meta-analysis, looking at rates of natural progression to diabetes in high-risk individuals, found that progression rates to diabetes in subjects exhibiting elevated fasting glucose, IGT, or both are roughly double those for normal glucose tolerance progressing to diabetes.[30,31] These results point to plasma glucose levels as a potential target to reduce progression to and hence prevalence of type 2 diabetes. Studies of pharmaceutical agents such as metformin,[32] acarbose,[33] and pioglitazone,[34] that all lower glucose levels, were found to lower diabetes mellitus onset in high-risk populations. However the high costs, side effects and difficult compliance issues of these interventions have slowed or blocked widespread implementation.

Cinnamon (肉桂 ròu guì) extract may offer a low cost, readily available and relatively easily implemented means of reducing plasma glucose levels and thereby reducing T2D. The present study

Table 2
Effects of placebo or supplementation with 250 mg water extract of cinnamon twice per day for two months in hyperglycemic adults.[a,b,c]

	Placebo			Cinnamon (肉桂 ròu guì)		
	n	Baseline	Final	n	Baseline	Final
BMI[d]	70	25.8 ± 0.3	25.6 ± 0.3	63	24.8 ± 0.4	24.6 ± 0.4
Fasting glucose, *mmol/L*	73	8.57 ± 0.32	8.44 ± 0.34	64	8.85 ± 0.36	8.19 ± 0.29**
2-hr glucose, *mmol/L*	73	14.18 ± 0.60	13.74 ± 0.58	64	15.09 ± 0.57	13.30 ± 0.55***
Fasting insulin, *mU/L*	72	21.64 ± 1.66	23.65 ± 3.02	63	24.25 ± 2.01	22.26 ± 2.08*
2-hr insulin, *mU/L*	73	86.43 ± 5.19	82.58 ± 4.84	59	93.13 ± 5.78	83.17 ± 4.53
HOMA-IR	72	8.51 ± 0.80	9.12 ± 1.32	63	9.67 ± 0.90	8.32 ± 0.84**
Fructosamine, *μmol/L*	57	348 ± 9	338 ± 8	51	336 ± 8	319 ± 7*
Systolic blood pressure, *mmHg*	72	122.7 ± 1.5	126.2 ± 1.8¤	63	128.3 ± 1.9	131.1 ± 1.9
Diastolic blood pressure, *mmHg*	72	75.9 ± 0.9	77.4 ± 1.0	63	78.2 ± 1.1	77.2 ± 1.1
Total cholesterol, *mmol/L*	57	5.12 ± 0.12	5.05 ± 0.14	53	5.20 ± 0.14	4.96 ± 0.16*
LDL cholesterol, *mmol/L*	57	3.45 ± 0.09	3.35 ± 0.11	53	3.48 ± 0.14	3.25 ± 0.14**
HDL cholesterol, *mmol/L*	57	1.28 ± 0.04	1.21 ± 0.04¤¤	53	1.26 ± 0.04	1.17 ± 0.04**
Triacylglycerols, *mmol/L*	57	2.05 ± 0.17	2.48 ± 0.19¤¤¤	53	2.20 ± 0.21	2.58 ± 0.28*

[a] Mean ± SEM.
[b] Placebo group – significantly different from baseline ¤p < 0.05; ¤¤p < 0.005; ¤¤¤p < 0.0001.
[c] Cinnamon group – significantly different from baseline *p < 0.05;**p < 0.005;***p < 0.0001.
[d] BMI = Body Mass Index.

used a well-controlled and defined parallel study design to carefully characterize the response of plasma glucose metabolism in Chinese adults with hyperglycemia to daily consumption of a well-defined, spray-dried water-extract of cinnamon. Study participants were hyperglycemic and 70% were overweight or obese based on the Chinese standards for BMI.[26] Recent research suggests that adipose tissue is an active endocrine organ that releases cytokines and contributes to inflammation and ultimately to insulin resistance.[35–37] In our study, fasting insulin was twice as high in the group with BMI above 28 compared to the group with BMI less than 24. Likewise, insulin resistance estimated by HOMA-IR and triacylglycerols were significantly elevated in the overweight and obese BMI groups and BMI was correlated with diastolic blood pressure, fasting insulin and triacylglycerols.

Meeting the criteria for metabolic syndrome was not required for participation in this study; thus, no measure of central obesity was taken. However, many of the men and women had lipid and blood pressure values consistent with metabolic syndrome in addition to their elevated fasting glucose. Specifically, 40% of the men and women had inappropriately low HDL-cholesterol, 53% had triglycerides above 1.7 mmol and 46% had systolic or diastolic blood pressure above 130/85.[38]

Mechanisms by which cinnamon or cinnamon extract supplements lower glucose, insulin and estimates of insulin resistance are not yet completely clear, but food composition analyses, in vitro, animal, and human studies suggest possibilities. Proanthocyanidins, which are high in cinnamon, are plant metabolites with antioxidant activity.[39] Cinnamon has a particularly high hydrophilic oxygen radical absorbance capacity (ORAC)/total phenolics ratio.[23] Furthermore, cinnamon bark extracts inhibited the formation *in vitro* of advanced glycation end products (AGEs) which contribute to diabetic complications. This inhibition has been attributed to the ability of phenolic compounds in the extracts to trap reactive carbonyl species.[40] Antioxidant variables, ferric reducing antioxidant potential and plasma thiols, increased while plasma malondyaldehyde (MDA) levels decreased in subjects receiving a cinnamon extract similar to the one used in this study.[5]

In tests of insulin activity using the rat epididymal fat cell assay, cinnamon extracts produced the greatest enhancement of glucose utilization of all the forty-nine herb, spice, and medicinal plant extracts tested.[20] Subsequently, water-soluble polyphenolic polymers from cinnamon were found to increase insulin activity by approximately twenty-fold in the same assay.[19]

Several steps in insulin signaling pathways are affected by cinnamon extracts. Various cinnamon compounds effect protein phosphorylation-dephosphorylation reactions in adipocytes.[21,22] Another study suggested that a cinnamon extract affects a tyrosine phosphatase that would otherwise inactivate the insulin receptor[21] and Cao and coworkers reported that a water extract of cinnamon increased insulin-dependent glucose transporter 4 (GLUT4). Cheng et al[41] reported that water soluble cinnamon polyphenols inhibited glucose production that was accompanied by decreased expression of phosphoenolpyruvate carboxykinase and glucose-6-phosphatase, major regulators of hepatic gluconeogenesis. Inflammatory processes also contribute to insulin resistance.[36,37] The anti-inflammatory protein, tristetraprolin (TPP), is increased by cinnamon extracts.[24] TPP is reduced in obese people with metabolic syndrome, but both TPP mRNA and protein levels are increased by cinnamon.[25] A cinnamon extract seems to have the potential to increase proteins involved in insulin signaling, glucose transport, and the anti-inflammatory responses and decreases those involved in gluconeogenesis.

Beneficial effects of cinnamon extract may also derive from interactions with peroxisome proliferator-activated receptor gamma (PPARγ), a regulator of adipogenesis and insulin sensitivity. Considerable effort has been focused on drugs that would serve as ligands for this receptor.[42] Mueller and Jungbauer noted that cinnamon extracts bound PPARγ in competitive ligand binding assays.[43] Kim and Choung suggest that cinnamon regulates insulin sensitivity by regulating PPAR-mediated glucose metabolism.[44]

Qin et al[45] reported a significantly higher glucose utilization rate in animals fed a cinnamon extract compared to the rate in control rats. They suggested that cinnamon extract may improve insulin action via increasing glucose uptake, perhaps through enhancing the insulin-signaling pathway in skeletal muscle.

More investigation is needed of dietary factors involved in control of glucose homeostasis. Insulin resistance seems to be a common factor in virtually all markers for metabolic syndrome. Obesity is associated with low-grade inflammation, but cinnamon extract may have a role in reducing pro-inflammatory factors that promote insulin resistance. Moreover, cinnamon and cinnamon extract are rich sources of proanthocyanins that may be particularly effective in quelling inflammatory compounds and stimulating insulin signaling pathways.[25,46]

The unexpected increase in triacylglycerols is not consistent with any of the previous studies and is likely due to unidentified dietary changes since it was present in both the treatment and placebo groups.

5. Conclusion

This study documents the beneficial effects of 500 mg of a cinnamon (肉桂 ròu guì) extract per day on Chinese adults with elevated blood glucose. The cinnamon extract used in this study was a commercially available spray-dried water extract of cinnamon (CinSulin®) containing more than 4% of type A procyanidin polyphenols which are associated with improvements in insulin potentiating, antioxidant and anti-inflammatory activities. As demonstrated by this and related studies, cinnamon extract should be considered for the prevention and alleviation of elevated blood glucose thereby likely reducing progression to type 2 diabetes and its associated morbidity and mortality.

Conflicts of interest

None.

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Authors contributed to the study and manuscript in the following ways: Patient recruitment and sample collection and management (ZZ, RL, XG, QG, JZ, JK); laboratory analyses (ZZ, RL, XM); statistical analyses (XG, QG, BJS); drafting and revision of manuscript (BJS, PAD, RAA); review of manuscript (All).

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