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File: ■ Cinnamon (*Cinnamomum verum* syn. *C. zeylanicum*) ■ Diabetes

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RE: Meta-analysis of the Effects of "True Cinnamon" on Diabetes in Rats

Ranasinghe P, Jayawardana R, Galappaththy P, Constantine GR, de Vas Gunawardana N, Katulanda P. Efficacy and safety of 'true' cinnamon (*Cinnamomum zeylanicum*) as a pharmaceutical agent in diabetes: a systematic review and meta-analysis. *Diabet Med*. December 2012;29(12):1480-1492.

Diabetes mellitus is a leading cause of morbidity and mortality worldwide, and 90% of the cases are of the type 2 variety. Lack of compliance with complex drug regimes and inadequacies in those regimes are driving a strong usage of complementary and alternative medicines that includes herbal products.

Cinnamon (Ceylon cinnamon, true cinnamon; *Cinnamomum verum* syn. *C. zeylanicum*) is indigenous to Sri Lanka and has demonstrated antidiabetic effects. It is preferred over Chinese cinnamon (cassia; *Cinnamomum aromaticum*) because of its much lower levels of coumarin, which has strong anticoagulant, carcinogenic, and hepatotoxic properties. While there are reviews of the benefits of *C. aromaticum* on diabetes, there are no reviews on *C. verum* syn. *C. zeylanicum* in this regard. This paper reports on a systematic evaluation and meta-analysis of the literature on the effects of *C. verum* syn. *C. zeylanicum* extract on diabetes and its potential toxic effects.

The review was undertaken in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. The databases searched included PubMed, Web of Science, Biological Abstracts, SciVerse Scopus, SciVerse ScienceDirect, CINAHL, and The Cochrane Library for papers published before August 1, 2011. Meta-analyses were performed if there were 3 or more studies reporting on a given parameter. Such parameters included weight loss (WL), fasting blood glucose (FBG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), triglycerides (TGs), and insulin.

Sixteen studies met the inclusion and exclusion criteria, which included 5 in vitro studies, 6 in vivo animal studies (in Wistar rats with induced diabetes), and 5 in vivo/in vitro studies. There were no human studies found. Studies included acute and chronic (10-60 days) designs. Authentication of the cinnamon was performed in only 6 out of 16 studies.

In vitro Effects

- Inhibition of sucrase and pancreatic α-amylase with IC_{50} (half maximal inhibitory concentration) values of 0.42 ± 0.02 mg/ml and 1.23 ± 0.02 mg/ml, respectively; a synergistic effect was seen when acarbose was added
- Strong dose-dependent, competitive, and reversible inhibition of α-glucosidase
- Strong inhibition of α-amylase
- Restoration of pyruvate kinase and phosphoenolpyruvate carboxykinase activity in the liver and kidneys with cinnamon and glibenclamide treatment in diabetic rats
- Prevention of increases in glucose-6-phosphatase, glucose-6-phosphate dehydrogenase activity, and fructose-1,6-bisphosphatase in fructose-fed rats
- Doubling of glucose uptake in adipocytes, but a decrease in the presence of insulin
- Stimulation of glucose transporter-4 production and its translocation to plasma membrane
- Increase of hepatic glycogen content to a greater extent than glibenclamide
- Stimulation of insulin release from islet cells
- Activation of the phosphorylation of the insulin receptor β-subunit

In summary, cinnamon reduced postprandial intestinal glucose absorption by inhibiting pancreatic α-amylase and α-glucosidase, stimulating cellular glucose uptake by membrane translocation of glucose transporter-4, stimulating glucose metabolism and glycogen synthesis, inhibiting gluconeogenesis, stimulating insulin release, and potentiating insulin receptor activity.

In vivo Effects – Meta-analyses

The meta-analysis of WL studies (n=3) showed that cinnamon attenuated WL associated with diabetes in rats (random effects analysis=15.79; 95% confidence interval [CI]: 6.39, 25.19; P=0.001). The meta-analysis of FBG studies (n=6) also showed significant reductions (P<00001); however, statistical heterogeneity of the data prevented the evaluation of a pooled estimate. The meta-analysis of TC studies (n=4) did not show a consistent reduction. HDL-C studies (n=5) showed a significant increase and TG studies (n=4) showed a significant decrease with treatment; however, these studies also had significant heterogeneity, preventing further evaluation. Serum insulin studies (n=3) showed an increase.

In vivo Effects

- Significant decrease in low-density lipoprotein cholesterol (LDL-C) compared with untreated diabetic rats (P<0.01)
- Reduction in hemoglobin A1c (HbA1c) levels to an equal degree as glibenclamide
- Decrease in FBG, HbA1c, homeostatis model assessment of insulin resistance (HOMA-IR), TC, TGs, free fatty acids, and phospholipids in fructose-fed rats that were fed cinnamon compared to those not fed cinnamon
- Reduction of the total glycemic response upon sucrose loading
- Dose-dependent increase of the nociceptive (pain) threshold in alloxan-induced diabetic neuropathy

- Protection from negative effects on the kidney as evidenced by decreased levels of liver enzymes

Safety

- Acute safety studies found no behavioral or biochemical changes at up to 20 times the normal dose
- The 50% median lethal dose value (LD_{50}) was 1850 ± 37 mg/kg; extrapolating this to humans would make the LD_{50} 11.4 ± 0.2 g/kg
- Normal levels of liver enzymes and the proper weight of the liver were restored in streptozotocin-induced diabetic rats

Aside from the direct effects of cinnamon as described above, its phenolic components additionally bring antioxidant properties, which may be effective in reducing atherogenesis and its progression. Cinnamon also has anti-inflammatory properties. The studies reviewed in this paper showed better glycemic control and healthier lipid parameters, reduction of insulin resistance, potentiation of the action of insulin, and amelioration of common complications associated with diabetes in rats, in addition to a strong safety profile. Randomized, double-blind studies should be undertaken to establish efficacy and safety in humans.

—Risa Schulman, PhD

The American Botanical Council has chosen not to reprint the original article.