Effects of the polyphenol content on the anti-diabetic activity of *Cinnamomum zeylanicum* extracts

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*Cinnamomum zeylanicum* is a popular kitchen spice widely investigated for insulin potentiating effects. Though a group of water soluble polyphenols belonging to the oligomeric procyandins has been identified as the bioactive principle, the lack of systematic information on the effect of the polyphenol content on safety and anti-diabetic efficacy remains as a major limitation for the development of optimized and standardized cinnamon extracts for functional use. In the present paper, water soluble extracts of *Cinnamomum zeylanicum* containing 45 and 75% gallic acid equivalents (GAE) of polyphenol content were prepared by a novel process and characterized by tandem mass spectrometry. The polyphenol enhanced extracts were shown to be safe and offered better antioxidant potential, hypoglycemic effect, hypolipidemic effect, and significant decrease in other biochemical parameters as compared to the standard aqueous extract containing 15% GAE, when administered to streptozotocin-induced diabetic rats at 200 mg per kg b.w. for 30 days. The efficacy of polyphenol extracts in lowering blood glucose levels and ameliorating oxidative stress was further demonstrated in humans by administrating *procynZ-45* containing 45% GAE polyphenols at a relatively low dosage of (125 mg x 2) per day for 30 days to 15 volunteers who had elevated fasting blood glucose levels; but not involved in any medication.

1. Introduction

Control over the blood glucose level is important for avoiding the complications associated with diabetes mellitus (DM), a complex multifactorial disorder characterized by high blood glucose level (hyperglycemia) and glycosuria resulting from the dysfunction of pancreatic β-cells and insulin resistance.1,2 Despite the extensive research on prevention and control, the prevalence of DM is growing at an alarming rate, especially the type 2 DM which accounts for 90–95% of all cases of diabetes.1 Though the lifelong administration of synthetic anti-diabetic drugs has been widely accepted as the treatment of choice, intervention of safe hypoglycemic plant extracts together with a little change in lifestyle has been recognized as the best approach.3 Since synthetic drug based intervention regimes are largely limited due to associated toxicities,4,5 safe hypoglycemic botanicals derived from food components such as GRAS-listed (generally regarded as safe) fruits, vegetables and culinary spices as demonstrated by their bioactivities such as insulin potentiating, insulin sensitizing, insulin mimetic, etc. are of great significance.

The inner bark of *Cinnamomum* species and their aqueous extracts have been widely investigated for antidiabetic properties.2,5 Though the hypoglycemic effect of the essential oil of cinnamon and its various constituents such as cinnamaldehyde, eugenol, coumarin and cinnamic acid were known, the insulin potentiating activity of the aqueous extracts was shown to be due to a group of water soluble polyphenols belonging to the class of oligomeric procyanidin type A polymers.6 Aqueous extracts were subsequently investigated in detail and shown to increase in vitro glucose uptake and glycogen synthesis, increase phosphorylation of the insulin receptor, potentiate the in vitro activity of insulin, enhance insulin-regulated glucose utilization and decrease high fat induced insulin resistance.3,7 Several human intervention studies, including meta-analysis, have also demonstrated the anti-diabetic and anti-hypertensive benefits of cinnamon extracts.5,7–10 However, a few studies have also reported the non-beneficial effect of cinnamon extracts in the blood glucose levels of specific populations such as Type1 DM patients, among non-insulin dependent Type2 DM patients and among postmenopausal Type2 DM subjects.11–13

Despite all the above mentioned beneficial effects of various *Cinnamomum* species and their aqueous extracts, no systematic investigations have so far been reported to standardize the extracts with respect to a biomarker and further to investigate...
Enhanced anti-diabetic activity of polyphenol-rich de-coumarinated extracts of Cinnamomum cassia

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ABSTRACT

Although the insulin potentiating activity of Cinnamomum cassia extracts has been studied in detail, no systematic investigations have so far been reported to standardize those extracts with respect to their bioactive polyphenol and toxic coumarin contents. Moreover, no process has been reported for the preparation of de-coumarinated water-soluble polyphenol-rich extracts of cinnamomum species. In the present contribution, we describe the preparation of de-coumarinated polyphenol-rich extracts of Cinnamomum cassia containing 45 and 70% gallic acid equivalents of polyphenol content and their characterization by tandem mass spectrometry. These extracts were investigated for their relative anti-hyperglycaemic effects in comparison with a standard aqueous extract containing 18% polyphenol content and 0.8% coumarin. De-coumarinated extracts were found to be safe and showed 3.4 fold enhancements in relative lowering of blood sugar levels as compared to the standard cinnamon extract, when administered to streptozotocin-induced diabetic rats at 200 mg/kg body weight for 30 days.

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1. Introduction

Diabetes mellitus (DM) is a complex multifactorial disorder of glucose intolerance resulting from the dysfunction of pancreatic β-cells and insulin resistance (Bedekar, Shah, & Koffas, 2010). In spite of the several approaches for effective control of hyperglycaemia are in practice, this metabolic disease has marked an alarming growth rate and is predicted to account for more than 350 million cases by 2030 (Sarah, Gojka, Anders, Richard, & Global, 2004). While practicing the lifelong administration of synthetic anti-diabetic drugs along with a little change in life style as the best available treatment of choice, the Expert Committee of World Health Organization (WHO) has recommended investigations to derive safe anti-hyperglycaemic agents of plant origin, owing to the side effects associated with the synthetic drugs (Alarcon-Aquilara, Roman-Ramos, Perez-Gutierrez, Aguilar-Contreras-Weber, & Flores-Saenz, 1998). Though substantial numbers of plants with hypoglycaemic effects are known in traditional medicine, standardized hypoglycaemic extracts of edible plant components such as fruits, vegetables and kitchen spices capable of ameliorating blood sugar levels are of great significance.

Among the various phytochemicals identified as having anti-diabetic properties, polyphenols constitute an important group because of their wide range of pharmacological effects (Coman,