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Role of cinnamon as beneficial antidiabetic food adjunct: a review

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ABSTRACT

Diabetes mellitus (DM) is the most common of the endocrine disorders. It is an important human ailment, afflicting many, from various walks of life in different countries. Insulin is the ideal treatment for diabetes in the conditions where blood glucose levels cannot be controlled. The introduction of insulin and oral hypoglycemic agents has revolutionized the management of diabetes. Despite advances in drug management of diabetes, the adverse drug effects have made scientists to look towards hypoglycemic agents of plant origin, especially in the developing countries. It is postulated that spices play a major role in the management of diabetes. Spices are a group of esoteric food adjuncts that have contributed to taste and flavor of foods for thousand of years. Cinnamon is one such spice, which has the potential to attenuate the development of diabetes and its complication. It also does not have much troublesome side effects. The present paper reviews the outstanding ability of cinnamon, to tackle diabetes by boosting insulin function. It also points to the areas of future research, to further control many of the pathological mechanisms that cause diabetes.

Keywords: Cinnamon, Hypoglycemia, Spices, Type 2 Diabetes Mellitus.

INTRODUCTION

The word “diabetes” is derived from the Greek word “diabainein” which means “to flow through”. Diabetes mellitus (DM) is a complex and multifarious group of disorders that is a major source of ill health in the world [1]. DM is defined as a state in which homeostasis of carbohydrate and lipid metabolism is improperly regulated by insulin. DM exists in two major forms: type 1 or insulin dependent diabetes mellitus (IDDM) and type 2 or non-insulin dependent diabetes mellitus (NIDDM).Type 2 DM is the most common form of diabetes, accounting for around 90 to 95% of all diabetic patients. According to recent estimates, the human population worldwide appears to be in the midst of an epidemic of diabetes. The total number of people with diabetes is projected to rise from 171 million in 2000 to 366 million in 2030 [2]. Type 2 DM is a

metabolic disorder characterized by chronic hyperglycemia (elevated levels of plasma glucose), caused by inherited and/or acquired deficiency in the production of insulin by the pancreas, or by the ineffectiveness of insulin produced. The condition causes deregulation of carbohydrate, protein, fat metabolism. Besides hyperglycemia, several other factors including dislipidemia or hyperlipidemia are involved in the development of micro- and macro-vascular complications of diabetes, which are major causes of morbidity and death [3-5].

Escalation in prevalence of diabetes appears to be more pronounced in developing countries. The World Health Organization (WHO) has estimated that in 1995, 19.4 million individuals were affected by diabetes in India. These numbers are expected to increase to 57.2 million by the year 2025. The revised figures are 80.9 million by the year 2030 [6]. Studies on native Indian population have confirmed that during last 30 years, the patients with diabetes have risen markedly. The disease is affecting at an alarming rate to both rural and urban populations in India [7-10]. The recent increase is attributed, to some extent, to industrialization, urbanization and their associated life style changes, physical inactivity, obesity and possibly a genetic predisposition [2].

Treatment of Diabetes

DM is a disorder that cannot be cured, but can only be managed. Pharmaceutical companies have developed many drugs (e.g. thiazolidinediones) to combat type 2 DM [11]. In spite of tremendous progress in the management of diabetes using synthetic drugs, potential new inexpensive treatments should be used to reduce global morbidity and mortality, as most of the people with type 2 diabetes lives in areas of the world, where existing treatments are unavailable or are too expensive. In the treatment of DM, non-pharmacologic measures (diet, exercise and weight loss) remain a critical component of therapy. It is well documented that insulin sensitivity can be modulated by various dietary compounds and exercise regimes [12-14]. Dietary management includes, use of traditional medicines that are mainly derived from plants [15]. The WHO has recommended that this practice should be encouraged, especially in developing countries [16]. The ethnobotanical information reports that 800 plants possess anti-diabetic potential [17]. A number of articles have been reported on plants screened for hypoglycemic activity [18-22]. But very few traditional antidiabetic plants have received proper scientific validation. Moreover, a scientific proof of the antidiabetic activity of medicinal plants and phytopharmaceuticals with fewer side effects is still lacking.

Spices and diabetes mellitus

Spices are the common dietary adjuncts that contribute to the taste and flavor of foods. Spices are pungent or aromatic substances obtained from dried parts of plants usually seeds, fruits, leaves, roots, bark and other plant parts originating in the tropics. Plant seeds, fruits, leaves and bark contain polyphenols and are thus used as additives to flavor, color or preserve food. But spices can fulfil more than just this function in the foods to which they are added. They are sources of many bioactive compounds that can influence digestion and metabolism processes. Research displays several beneficial physiological effects of spices, including their insulin-potentiating activity in normal as well as experimentally induced diabetic animal models, and also in humans [23-25]. One spice that is emerging as a potential therapeutic agent for the management of diabetes is cinnamon.

Cinnamon

Cinnamon is amongst the world's oldest and most frequently consumed spices, and is used as an herbal remedy [26-28]. The medicinal use of this plant has been documented in Ayurveda (the Indian system of medicine), for over 6000 years. The genus *Cinnamomum* consists of 250 species of aromatic evergreen trees and shrubs, primarily located in Asia and Australia. The term Cinnamomum is derived from Greek *kinnamomon*, meaning "sweet wood". Cinnamon is classified in the botanical division: Magnoliophyta, class: Magnoliopsida, order: Magnoliales and family: Lauraceae. The cinnamon of commerce is the dried inner stem-bark of a small evergreen tree 10-15 meters tall. It is native to tropical southern India and Srilanka. There are two types of cinnamon, common cinnamon (vernacular name: dalchini) or true cinnamon (*Cinnamomum zeylanicum*, *C. verum*) and cassia (*Cinnamomum aromaticum*).

Cinnamon has been used for centuries, as flavor modifiers to make food more palatable. Its ingredients impart characteristic flavor and spicy aroma to food. The range of variation in the general composition of various cassia barks as observed by researchers is as follows: moisture (6.5-11.9%), crude fibre (12.0-28.8%), carbohydrate (6.9-32.0%), protein (3.1-3.4%), fixed oil (0-2.1%), volatile oil (0.5- 5.1%), and cold alcohol extract (4.6-16.7%) [29]. Among these, the constituent of commercial importance is the volatile oil. Volatile components are present in all parts of cinnamon and can be classified broadly into monoterpenes, sesquiterpenes and phenylpropenes. Cinnamaldehyde (more precisely *trans*-cinnamaldehyde or 3-phenyl-2-propenal) (Fig.1) is the main constituent in cinnamon bark oil, whereas, that of leaf oil is eugenol [30, 31].

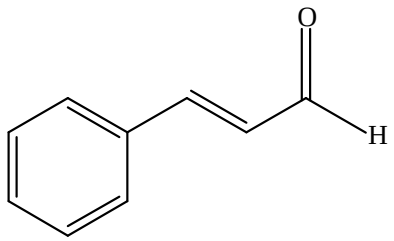

Fig. 1 Cinnamaldehyde from Cinnamomum zeylanicum bark oil

The physico-chemical properties of ceylon cinnamon bark and leaf oil are indicated in Table 1 [32]. The cinnamon bark oil has a delicate aroma along with a sweet pungent taste.

Table 1. Physico-chemical properties of ceylon cinnamon

Property	Bark Oil	Leaf Oil
Specific gravity (20°C)	1.010-1.030	1.030-1.050
Optical rotation (°) (20°C)	Slightly laevorotatory	1° 96' – 0° 40'
Refractive index (20°C)	1.573 - 1.591	1.529- 1.537
Aldehyde content	65-76%	4%
Eugenol content	4-10%	77.3-90.5%
Solubility characteristics	Soluble in 2-3 volumes of 70% alcohol	Soluble in 1.5 volumes of 70% alcohol

The major compounds in bark oil are cinnamaldehyde (75%), cinnamyl acetate (5%), caryophyllene (3.3%), linalool (2.4%) and eugenol (2.2%) [33]. Cinnamon leaf oil has a warm,

spicy and somewhat harsh odour, lacking the smooth consistency of cinnamon bark oil. The principal component of leaf oil, namely, eugenol varies from 65-92% (Fig. 2) [33]. Although it is always cinnamaldehyde and eugenol, with other minor components, the chemical composition of cinnamon varies considerably depending on the location and method of distillation.

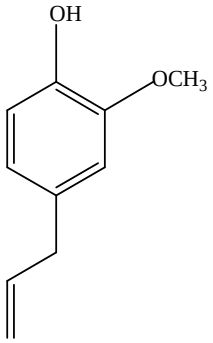

Fig. 2 Eugenol from Cinnamomum zeylanicum leaf oil

Cinnamon has been shown to be generally safe when ingested. Common and cassia cinnamon has recently been the subject of intense research and have been granted GRAS (generally recognized as safe) status by the United States Food and Drug Administration (USFDA), as a food additive. Extensive investigation in recent years suggests that cinnamon possess numerous pharmacological activities including antioxidant [34-37], antimicrobial [38-42], antipyretic [43], antiulcerous [44, 45], antiallergic [46, 47] and anti-inflammatory effects [48, 49]. More recently, scientific attention has also been paid to the insulin potentiating capabilities of cinnamon, which may prove beneficial for diabetic patients. In the present review, current evidences, from recently published animal experimentation, as well as clinical trials where cinnamon, its extracts, or its active chemical components were examined, as a marker of glucose tolerance in people with diabetes and insulin resistance, will be highlighted. The review also provides a basis for a full-scale investigation of the therapeutic potential of cinnamon.

Cinnamon as an Antidiabetic Agent

Interest in cinnamon as a potentially useful treatment for type 2 diabetes began almost 20 years ago. In 1990, Khan et al. isolated an unidentified factor from cinnamon and termed it as insulin-potentiating factor (IPF). They demonstrated that IPF may be involved in the alleviation of the signs and symptoms of diabetes, and other diseases related to insulin resistance [50]. The potential role of cinnamon has been shown in several *in vitro*, animal and human studies.

In vitro studies

Broadhurst et al. compared 49 herbs, spices and medicinal plant extracts for their insulin-like or insulin-potentiating action in an *in vitro* model [51]. The aqueous extracts of cinnamon potentiated insulin activity more than 20-fold, higher than any other compound, tested at comparable dilutions *in vitro* in the epididymal fat cells. Cinnamon extracts showed to improve insulin receptor function by activating the enzyme that causes insulin to bind to cells (insulin-receptor-kinase) and inhibiting the enzyme that blocks this process (insulin-receptor-phosphatase), leading to maximal phosphorylation of the insulin receptor, which is associated with increased insulin sensitivity [52]. Anderson et al. characterized the unidentified factor present in cinnamon as methylhydroxychalcone polymer (MHCP) and investigated its ability to

function as insulin mimetic in 3T3-L1 adipocytes [53]. The study analyzed that MHCP stimulated the autophosphorylation of the insulin receptor (IR), upregulated glucose uptake, glycogen synthesis and glycogen synthase (GS) activity in 3T3-L1 adipocytes, and downregulated glycogen synthase kinase-3β (GSK-3β) activity. Glycogen synthesis stimulation is through a class I phosphatidylinositol (PI) 3-kinase dependent pathway. These events are all characteristic of 3T3- L1 adipocytes response to insulin. Moreover, the responses observed during the dual treatment were greater than additive, indicating synergism between the two compounds. Anderson et al. demonstrated that the *in vitro* insulin-potentiating activity found in cinnamon was present in the aqueous fraction. They suggested that the major active components in cinnamon are water soluble doubly-linked procyanidin type – A polymers (Fig. 3), which were likely misidentified as MHCP in earlier studies [54]. These polyphenolic compounds present as monomers or oligomers are responsible for *in vitro* insulin enhancing activity in epididymal fat cells.

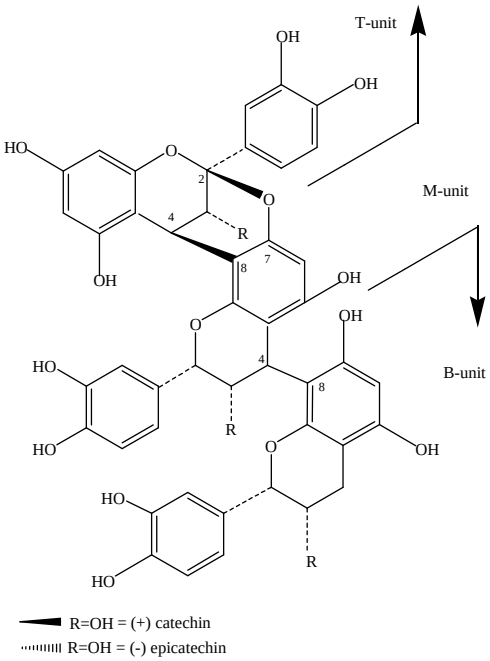

Fig. 3 Structure of doubly-linked procyanidin type–A polymer found in cinnamon that enhances insulin activity

Animal studies

Besides *in vitro* studies, several animal studies have also reported insulin-potentiating effects after cinnamon administration. *In vivo*, administration of aqueous extracts of cinnamon improves glucose metabolism and potentiates the action of insulin. Euglycemic clamp studies have shown that after 3 weeks of oral administration of an aqueous cinnamon extract at 30 and 300 mg/kg body weight (BW), there is enhanced glucose utilization in rats, in a dose-dependent fashion. Skeletal-muscle insulin stimulated insulin receptor (IR)-β, IR substrate (IRS)-1 tyrosine phosphorylation levels and IRS-1 association with phosphatidylinositol (PI) 3-kinase are also increased. These results suggest that increased glucose uptake *in vivo* is a result of enhancing of the insulin signaling pathway [55]. Cinnamon extract fed to high fructose-induced insulin resistant male Wistar rats indicated that insulin stimulated glucose uptake was significantly greater in cinnamon fed rats and that the rate of insulin resistance was reversed by cinnamon

feeding [56]. Kannappan et al. also demonstrated that glucose tolerance and insulin sensitivity improved by cinnamon bark extract (CBEt) treatment significantly by increasing the decreased activity of hexokinase and glycogen content in the liver and skeletal muscle of high fructose diet (HFD) fed rats [57]. Kim et al. studied the effects of cinnamon extract on blood glucose after 2, 4 and 6 weeks in db/db mice, a type 2 diabetic model [58]. The blood glucose concentration significantly decreased in a dose-dependent manner. The concentration of triglyceride, total cholesterol and intestinal α-glycosidase activity were significantly low after 6 weeks of the administration. The hypoglycemic and hypolipidemic effects of cinnamaldehyde from *Cinnamomum zeylanicum* was investigated in streptozotocin (STZ)-induced diabetic rats [59]. Cinnamaldehyde was administered at different doses (5, 10 and 25 mg/kg bw) for 45 days to (STZ)-induced male diabetic Wistar rats. The plasma glucose concentration decreased significantly in a dose-dependent manner. In addition, the serum total cholesterol and triglyceride levels also decreased. Several recent studies have also indicated that administration of cinnamon oil or polyphenolic oligomer rich extracts of cinnamon have valuable antihyperglycemic, hypolipidemic and antioxidant effects in STZ-induced diabetic rats [60, 61]. The mode of action for this hypoglycemic effect may be attributed to an increase in serum insulin levels, hepatic glycogen storage [59] or insulin-receptor signaling [56], an insulino-mimetic effect [62] or a reduction in intestinal α-glycosidase activity [58]. Verspohl et al. evaluated blood glucose and plasma insulin levels in rats using both common and cassia cinnamon bark or extracts. The study concluded that cassia extract was superior to the common cinnamon extract [63]. On the basis of these studies cinnamon is well known for pharmacological properties in the treatment of type 2 diabetes.

Human studies

Following the observations that cinnamon potentiates insulin action *in vitro*, in 2003 Khan et al. conducted the first randomized, double-blind, placebo-controlled clinical trial to evaluate the effect of cinnamon in individuals on sulfonylurea drug therapy with type 2 diabetes [64]. Patients receiving insulin were excluded from the study. A total of 60 people with type 2 diabetes (30 males and 30 females) were divided randomly into six groups. The first three groups were given 1, 3 or 6 g of cinnamon as *Cinnamomum cassia* in pill form daily, while the other three groups consumed equivalent number of placebo capsules. The intervention lasted 40 days and was followed by a 20-day washout period. After 40 days, all participants in the group taking cinnamon were found to have reduced the mean fasting serum glucose (18-29%), triglycerides (23-30%), low density lipoprotein (LDL) cholesterol (7-27%) and total cholesterol (12-26%) levels. However, changes in high density lipoprotein (HDL) cholesterol were not significant. Those taking 6 g/day had reduced glucose levels after 20 days but only those taking 1 g/day maintained lower glucose levels 20 days after stopping the regimen. There were no significant changes in the placebo group. The study indicated benefit of cinnamon supplementation at low levels (1-6 g/day).

In a different randomized, double-blind, placebo-controlled study, Mang et al. investigated the effects of daily intake of an aqueous cinnamon extract (*Cinnamomum cassia*) in 65 German patients with well-controlled type 2 diabetes with mean baseline glycosylated haemoglobin (HbA_{1c}) of 6.8%, during the 4 months of intervention. Only patients treated with oral anti-diabetics or diet were included in the study. The 112 mg of aqueous cinnamon extract taken by patients corresponded to 1 g of cinnamon per day. The cinnamon extract had a moderate effect in

reducing fasting plasma glucose concentration by 10.3%, in the cinnamon group as compared to 3.4% in the placebo group. However, no significant changes in HbA_{1c}, total cholesterol, LDL, HDL or triacylglycerol were reported [65].

In a separate double-blind, placebo-controlled study involving 22 subjects with prediabetes and features of metabolic syndrome, effects of supplementation with a commercially available extract of cinnamon (Cinnulin PF®) on fasting blood glucose (FBG) and body composition was determined. The subjects were divided into two groups, and given either 500 mg/day of Cinnulin PF®, or a placebo for 12 weeks. The subjects in the group receiving Cinnulin PF® displayed decrease in FBG (-8.4%), systolic blood pressure (-3.8%) and increase in lean mass (+1.1%), compared with the placebo group. There were also significant decreases in body fat (0.7%) in the cinnamon group [66].

Wang et al. postulated that insulin-potentiating water-soluble polyphenol compounds found in cinnamon might be beneficial for women with polycystic ovary syndrome [67]. Polycystic ovary syndrome is one of the most common endocrinopathies among women of child-bearing age, affecting 5-10% of the population. Insulin resistance and the compensatory hyperinsulinaemia are present in 50-70% of the women with polycystic ovary syndrome, and may be as high as 95% in overweight women. In a small study, fifteen women with polycystic ovary syndrome were randomized to daily oral cinnamon and placebo for 8 weeks. The oral cinnamon extract resulted in a significant reduction in fasting glucose as well as in insulin resistance, with oral glucose tolerance tests (OGTT) also showing a 21% reduction in mean glucose and an increase in Matsuda's insulin sensitivity index. The cinnamon extract was found to improve insulin resistance of the women with polycystic ovary syndrome compared with the control women.

In another clinical trial, Solomon et al. [68] investigated effect of polyphenols from cinnamon on seven lean healthy male subjects, aged 26 ± 1 years, body mass index 24.5 ± 0.3 kg/m^2, with good glucose tolerance. The study showed that ingestion of 5 g of cinnamon reduced plasma glucose responses to OGTT and improved insulin sensitivity. Moreover, the effects of cinnamon on glucose tolerance and insulin sensitivity persist for 12 h after cinnamon ingestion suggesting that cinnamon may have prolonged effects on events associated with increased insulin sensitivity. A recent study by them involved eight male volunteers (aged 25 ± 1 years, body mass index 24.0 ± 0.7 kg/m^2), who underwent two 14-day interventions, involving cinnamon or placebo supplementation (3g/day) [69]. Cinnamon ingestion reduced the plasma glucose responses to OGTT and improved insulin sensitivity. However, the effects were lost following cessation of cinnamon feeding. The results show that cinnamon improves glycemic control and insulin sensitivity, but the effects are quickly reversed. Hlebowicz et al. also assessed in 14 healthy subjects (aged 25.6 ± 4.8 years with BMI of 22.6 ± 2.2 kg/m^2) by using crossover trial, the beneficial effects of the addition of 6 gm of cinnamon to a meal of rice pudding. Cinnamon significantly reduced postprandial blood glucose and delayed gastric emptying, without affecting satiety [70]. In a recent controlled trial by Crawford for adult patients of 3 primary care clinics at a U.S. military base, he randomized 109 patients with type 2 diabetes and HbA_{1c} greater than 7 to either usual care (n = 54), or usual care plus 1 gm of cinnamon per day (n = 55) for 90 days. 1 gm of daily adjunct cinnamon, in addition to usual care lowers HbA_{1c} by 0.83%, compared with usual care alone, which lowered HbA_{1c} by 0.37%. Thus, cinnamon can be useful for lowering HbA_{1c} in type 2 diabetics [71].

However, not all the clinical trials, regarding whole cinnamon or extracts of cinnamon have reported beneficial effects on fasting blood glucose in type 2 diabetes patients. Vanschoonbeek et al. in a placebo-controlled intervention study evaluated the potential benefits of cinnamon in 25 postmenopausal women, with stable type 2 diabetes on oral medications. The study was neither randomized nor blinded. Thirteen patients were given 1.5 g of cinnamon per day and 12 received placebo for 6 weeks. No significant differences were noted between groups in HbA_{1c} or fasting glucose levels [72]. Blevins et al. also observed no significant changes in a 3 months double blinded placebo controlled trial in 58 subjects with type 2 diabetes, who received 1 g cinnamon or placebo daily. Specifically blood glucose, HbA_{1c}, fasting lipids and insulin levels did not change [73]. In all the above studies, there have been no reported adverse effects and hence subjects with the poorest glycemic control appear to benefit from cinnamon.

Model of cinnamon effects

Strong evidence suggests that cinnamon polyphenols (CP) exhibit insulin-like activity in cells, animals and people with type 2 diabetes. To explore the molecular basis of insulin-like activity of cinnamon with doubly-linked procyanidin type-A polymers, Cao et al. investigated the effects of CP on the regulation of three of the proteins (insulin receptor β, glucose transporter 4 and tristetraprolin) involved in insulin signal transduction pathway, using mouse 3T3-L1 adipocytes. Based on these studies, he proposed a model [74], which shows that CP affects multiple steps related to glucose and insulin function. CP activates insulin receptor (IR) by increasing their tyrosine phosphorylation activity and by decreasing phosphatase activity that inactivates the insulin receptor [52].

CP increases the amount of insulin receptor β (IR β) and glucose transporter 4 (GLUT4) protein [74]. It increases glycogen synthase activity and glycogen accumulation with decreased glycogen synthase (GS) kinase-3 β (GSK3 β) activity [53]. CP also increases the amount of the anti-inflammatory protein, tristetraprolin (TTP) in the cells. All these activities and other potential activities may eventually lead to more efficient glucose transport and utilization. In addition, CP induced tristetraprolin accumulation may provide one of the molecular basis for the beneficial effects of cinnamon, in improving the condition of people, with diabetes by down regulating the synthesis of pro-inflammatory cytokines, as it binds to and subsequently promotes the degradation of those mRNAs encoding pro-inflammatory cytokines, such as tumor necrosis factor-α (TNF-α) and granulocyte-macrophage colony-stimulating factor (GM-CSF).

Adverse effects of cinnamon

In general, spices are generally recognized as safe when used in therapeutic doses. Spices produce adverse effects, especially when used in excessive amounts or in the long term. Some studies have reported minor adverse effects. The most common adverse effects reported with common and cassia cinnamon were related to contact irritation or allergic reaction with skin or mucus membranes [75, 76].

CONCLUSION

The paper demonstrates that cinnamon ameliorates the metabolism of glucose and lipids in patients with type 2 DM and may be used as an alternative for the treatment of diabetes. However, there is lack of scientific and clinical data to prove its efficacy and safety. Moreover,

the findings are somewhat mixed and inconclusive, particularly with regard to whole body insulin sensitivity. Thus, the question of whether its use might contribute to controlling the pandemic of type 2 diabetes worldwide remains unanswered. Hence, more rigorous, larger, population-based, randomized, clinically controlled trials with extended study length are required to further clarify use of cinnamon as a beneficial antidiabetic food adjunct. Future investigations regarding relationship between type form of procyanidin oligomers and anti-hyperglycemia activity in cinnamon species, its safety in pregnancy, its toxic effect could lead to the formulation of a dosage regimen and make it available as an alternative treatment option for diabetics.

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