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Review of Anti-Hyperglycemic Effect of *Tinospora crispa*

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Abstract

Tinospora crispa (Borapet or Wan kab hoi yai) is a climbing plant belonging to family Menispermaceae. In traditional medicine, an extract from the stems of *T. crispa* has been used for anti-hyperglycemic activity. The mechanisms of the anti-hyperglycemic actions of *T. crispa* are due to the stimulation of insulin secretion, enhancement of glucose utilization in peripheral tissues and reduction of hepatic gluconeogenesis. Borapetoside A and C are active ingredients for lower plasma glucose. In human studies, *T. crispa* extract possesses a significant anti-hyperglycemic effect in metabolic syndrome but this effect is abolished in type 2 diabetes mellitus. More clinical studies are recommended to evaluate the beneficial effect of *T. crispa* in human models.

Keywords: *Tinospora crispa*, borapet, borapetoside C, diabetes mellitus, anti-hyperglycemic effect

Introduction

Diabetes mellitus (DM), one metabolic disorder, has become a major public health problem and the prevalence has increased in the modern world, even in developing countries such as Thailand [1]. DM causes significant morbidity and mortality due to microvascular (retinopathy, nephropathy and neuropathy) and macrovascular (cardiovascular and cerebrovascular) complications [2,3]. There are several studies showing that diabetes is associated with abnormal insulin secretion and insulin sensitivity. Since insulin is the most important hormone in regulating glucose metabolism, impaired insulin secretion results in an increase in hepatic glucose production and reduction of glucose uptake in muscle. On the other hand, increased insulin resistance is a key feature in type 2 DM. It is characterized by a remarkable decrease in tissue glucose utilization in response to insulin [4]. The use of herbal remedies to treat DM has been documented since ancient times. Currently, more than 1,000 plant species are being used as folk medicines for DM throughout the world. The present review is an update on the anti-hyperglycemic effect of *Tinospora crispa.* This herb is a popular herbal medication that plays a role in the management of DM in Asian countries although the efficacy and adverse effects are still controversial.

Tinospora crispa or *T. crispa (Linn.) Miers ex Hook. F. & Thoms*., known in Thai as Borapet or Wan kab hoi yai is a climbing plant belonging to the family Menispermaceae [5]. A climber found in tropical and subtropical Asia such as India, Philippines, Indonesia, Malaysia, Vietnam and Thailand. It has various names such as Faridbuti or dier (Hindi), Makabuhai (Tagalog), Bratawali or Andawali (Indonesia), Dagadi (Malayalam) and Faridbel (Marathi). *T. crispa* has been widely used in Asia and Africa as a herbal remedy for a long time. In traditional medicine, an extract from the stems of *T. crispa* has been used for anti-inflammation [6], reducing thirst, increasing appetite, antipyretics, and anti-malarial effects [7]. In Malaysia, an aqueous extract of the *T. crispa* stem has been widely used and

claimed to be efficacious for treatment of DM. Moreover, some Thai diabetic patients have also traditionally used the decoction of *T. crispa* stem. The anti-hyperglycemic mechanisms of *T. cripsa* are due to the stimulation of insulin secretion, enhancement of glucose utilization in peripheral tissues and reduction the hepatic gluconeogenesis. Nevertheless, *T. crispa* has no supposed effect on intestinal glucose absorption [8].

The chemical constituents of *T. crispa* extracts have been extensively studied since the 1980s. The major active ingredients of *T. crispa* have been identified as terpenoids and terpenoid glycosides. The terpenoid glycosides are mainly composed of borapetosides A, B, C, D, E and F [9].

Animal studies

Noor *et al*. demonstrated that the water extract from *T. crispa* stems given to alloxan-induced diabetic rats by drinking water administration possesses a significant hypoglycemic and insulinotropic activity after one week. It also induced a dose-dependent stimulation of basal insulin secretion and potentiation of glucose-stimulated insulin secretion of isolated rat β cells, therefore the insulinotropic effect was proposed to be the mechanism of *T. crispa* [10]. Moreover, characterization of the insulinotropic effect of this decoction, using isolated human or rat islets of langerhans and HIT-T15 cells as an insulin-secreting cell model, revealed its influence on Ca^{2+} handling in β cells [11]. Also, it has been found that such insulin release at the basal condition may be mediated by closure of the voltage-dependent potassium adenosinetriphosphate (K_{ATP}) channels, facilitating β cell membrane depolarization, calcium entry into the cell, and insulin secretion. Noipha *et al*. studied the effect of aqueous extraction from *T. crispa* on glucose transport activity in the skeletal muscle cell line, L6 myoblast. This study demonstrated that *T. crispa* at 4 mg/ml significantly enhanced glucose uptake of L6 myotubes in a dose and time dependent manner with half maximum effects at 24 h. The effect of *T. crispa* on glucose uptake in skeletal muscle cells is comparable to troglitazone and metformin [12]. Lam *et al*. reported that a bolus intraperitoneal injection of borapetoside C at concentrations ranged from 0.5 - 5 mg/kg significantly stimulated insulin release and decreased plasma glucose in a dose-dependent manner in the non-diabetic and type 2 DM (diet-induced) mice, but not in type 1 DM (streptozocin-induced) mice. The plasma insulin level significantly increased to almost plateau at 3.0 mg/kg of borapetoside C administration in non-diabetic and type 2 DM mice, such an effect being comparable to that of glibenclamide (5 mg/kg). In the intraperitoneal glucose tolerance test, plasma glucose of non-diabetic and type 2 DM mice treated with borapetoside C were significantly lower than those of mice treated with the vehicle at 30, 60, 120 and 150 min after intraperitoneal glucose injection. The effect of borapetoside C on liver glucose synthesis in type 1 DM mice was examined by measuring the level of phosphoenolpyruvate carboxykinase (PEPCK). Treatment with borapetoside C (5.0 mg/kg, twice per day, for 7 days) caused a decrease in the PEPCK level comparable to that of the insulin-treated group. These results indicate that borapetoside C enhanced glucose utilization in peripheral tissues and reduced hepatic gluconeogenesis [13]. Ruan *et al*. found that borapetoside C from *T. crispa* significantly accelerated the glucose uptake and utilization in peripheral tissues in both normal and type 2 DM (diet-induced) mice after oral administration of glucose. Moreover, borapetoside C (5 mg/kg) also increased glycogen content in skeletal muscle and phosphorylation of insulin receptors and protein kinase B (Akt) as well as the protein levels of glucose transporter-2 (GLUT2) in liver. These results suggest that borapetoside C is not only a hypoglycemic agent, but can also act as an adjuvant for insulin function. Compared with the effect of insulin, borapetoside C induced more insulin receptor phosphorylation but less Akt phosphorylation and GLUT2 expression than insulin. This finding indicates that borapetoside C may bind to different sites of the insulin receptor and results in less efficient activation of Akt/GLUT2 signaling than insulin [9]. Furthermore, borapetoside A was shown the hypoglycemic effects that were mediated though enhance glucose utilization in peripheral tissues, to reduce hepatic glucose production and to activate the insulin secretion in type 2 DM mice [14]. Therefore, the active ingredients of *T. crispa* were borapetoside A and C that were mediated through both insulin-dependent and insulin-independent pathways.

Human studies

The efficacy of the *T. crispa* extract for treatment of diabetes has previously been verified in animal models. The anti-hyperglycemic effect of the *T. crispa* extract in human studies is still controversial. The *T. crispa* studies did not show efficacy for lowering plasma glucose or increasing plasma insulin in diabetic patients, whether or not respond to medication [15,16]. Sangsuwan *et al*. showed that *T. crispa* powder in capsule at a dosage of 1 g thrice daily for 6 months had no efficacy for treating patients type 2 DM who did not respond to an adequate dose of oral hypoglycemic drugs for at least 2 months and still had glycosylated hemoglobin of greater than 8.5 %. There were no significant changes in fasting serum glucose between that collected at baseline and during the study period in either group (250 and 245 mg/dl, respectively) or glycosylated hemoglobin (10.3 and 11.2 %, respectively) [15]. Klangjareonchai *et al*. demonstrated the areas under the curve of mean serum glucose and insulin levels in both healthy and diabetic participants were not significantly different between with or without *T. crispa* dry powder capsule. In type 2 DM participants, the area under the curve of glucose was slightly lower when 250 mg of *T. crispa* was ingested, but did not reach statistical significance (478 and 444 mg min/ml, respectively, $P = 0.57$) [16]. On the other hand, *T. crispa* extract possessed significant anti-hyperglycemic effect in metabolic syndrome. Sriyapai *et al*. showed that metabolic syndrome patients who received 250 mg twice a day of *T. crispa* dry powder capsule for 2 months had a significant decrease in fasting blood glucose from the baseline (median 8.00 mg/dL, $P < 0.01$) [17].

Adverse effect of *T. crispa*

The major adverse effect of *T. crispa* extract is liver toxicity. Furanoditerpenoids such as borapetosides have been identified in *T. crispa.* Animal studies revealed the formation of toxic metabolites from these furanoditerpenoids by cytochrome P450 3A. These toxic metabolites lead to hepatocyte death through the induction of apoptosis [18]. Sangsuwan *et al*. demonstrated that two from twenty patients who received *T. crispa* powder in capsule form at a dosage 1 g thrice daily for 6 months had a significant elevation of liver enzymes (aspartate aminotransferase and alanine aminotransferase) more than 3 times of the baseline values that returned to normal after discontinuation of the *T. crispa* capsule [15]. In another study, 16.7 % (6 patients) of subjects had elevated aspartate aminotransferase and alanine aminotransferase levels. In addition, simvastatin was used in 4 patients and 2 patients used atorvastatin [17]. Simvastatin and atorvastatin were metabolized by cytochrome P450 (CYP) 3A4, their risk of elevated liver enzyme were increased by inhibitor of CYP 3A4 [19]. *T. crispa* extract showed time-dependent inhibition of cytochrome P450 3A4 [18]. Taken together, risk of liver toxicity would be increased when use lipid-lowering drugs with *T. crispa* extract. In animal study, the high doses of *T. crispa* extract caused significant raising creatinine but no difference in renal histopathology [20]. Therefore, *T. crispa* extract should be avoid in liver and renal impairment and if signs of liver or renal toxicities occur while using *T. crispa* extract, the drug should be discontinued immediately.

Conclusions

Herbs are major sources of many drugs from ancient times. Pharmacological evaluations of herbs may lead to the discovery of new natural agents for treatment of diseases. *Tinospora crispa* is one of the herbs that have been used for different purposes in traditional medicine of Asia and Africa. Despite, the limitation of the study design, *T. crispa* appears to be associated with lower plasma glucose in metabolic syndrome patients. Randomized clinical trials are required to evaluate the efficacy of this herb. More clinical studies are recommended to evaluate the beneficial effects of *T. crispa* in human models.

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