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Banaba: The natural remedy as antidiabetic drug

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Abstract

Banaba (*Lagerstroemia speciosa* Pers) leaves has been used as tea or decoction type in the Philippines for blood sugar control and used in the treatment of diabetes in India and contain a treterpenoid compound know as a corosolic acid which can promote the absorption and utilization of glucose in the cell by transporting the stimulated glucose. As such, banaba plays a role in regulating levels of blood sugar and insulin in the blood. Banaba might decrease blood sugar but most of countries prefer to use diabetes medications even though they aware of serious side-effects. Additionally, various adverse effects are reported recently when many diabetic patients have been taken antidiabetic drugs in the long term. Here we reviewed whether banaba and corosolic acid can be replaced for current antidiabetic drugs through published several mechanisms of banaba and antidiabetic drugs, respectively. Consequently, banaba, one of medicinal herbs for antidiabetic effect surely can be functioned and can be a perfect candidate instead of antidiabetic drugs on lowering or maintaining normal blood sugar levels and prevention of diabetic complications without as well as treatment without any adverse effects.

Key words: *Lagerstroemia speciosa* diabetes blood glucose corosolic acid GLUT4 (glucose transporter)

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Introduction

Lagerstroemia speciosa Pers. (locally known as banaba in the Philippines) is widely distributed in most part of Philippines, India and Malaysia. Banaba includes several compounds such as corosolic acid and tannins, including lagerstroemin that have effects on the treatment of diabetes. These ingredients are thought to stimulate glucose uptake and have insulin-like activity. The latter activity is thought to be secondary to activation of the insulin receptor tyrosine kinase [1] or the inhibition of tyrosine phosphatase. That's why banaba is called "natural plant insulin".

The hot water leaves extract has reported to reduce diabetic symptoms in genetically diabetic KK-AY mice [2]. For past several years, banaba has been reported that various active ingredients isolated from *L. speciosa* leaves shows their hypoglycemic properties through increase the rate of glucose uptake or inducing glucose transport like insulin [3]. Glucose uptake is mediated in muscle mainly by the insulin-regulated glucose transporter (GLUT4). In the absence of insulin, this transporter slowly recycles between an intracellular storage compartment and the plasma membrane [4,5].

Corosolic acid, one of primary components from banaba extract induced GLUT4 (Glucose Transporter) translocation in diabetic mice [6]. The hypoglycemic effects from several human studies were shown with standard extract from *L. speciosa* leaves on 56 type II diabetic [7], with banaba tablet containing banaba extract on 24 mild type II diabetic patients [8], with banaba extract on 18 diabetic patients with one-year clinical study [9] and with corosolic acid on 31 subjects [10]. Unfortunately, many antidiabetic drugs are currently prescribing at hospitals and clinics over the world but recently various side effects were found and reported [11,12,13]. The alternative medicine from natural resource for diabetes or lowering of blood sugar level which has good efficacy without any side effects should be necessary because diabetes actually need long-term period management. In this short review paper, we review and compare with the mechanism of antidiabetic drugs and published hypoglycemic effects and those mechanisms of banaba. Therefore, we strongly recommend to pre-and diabetic patients that prior to taking a dose of antidibectic drugs have lots of side effects, it is the most valuable way to find the treatment or preventive way to maintain a normal blood glucose level and to prevent diabetic complications from natural resources.

Mechanism of antidiabetic drugs

The primary antidiabetic prescribing drugs can be classified in four groups: (a) drugs which indirectly increase insulin release; (b) drugs which activates directly insulin receptors; (c) drugs which act directly as inhibitors of glucosidase; (d) drugs which decreases the liver's glucose output. There are also major four different classes of antidiabetic drugs depend on different mechanisms: sulfonylureas, insulin-sensitizing agents, biguanides, and alpha-glucosidase inhibitors [14,15].

Sulfonylureas act by lowering blood sugar by stimulating the beta cells in the pancreas to release more insulin. Generally sulfonylureas are included Glucotrol (glipizide) and Amaryl (glimepiride) [16] but are reported various side effects such as hypoglycemia, upset stomach skin rash or itching and weight gain.

Insulin sensitizers function by improving the sensitivity to insulin and work with insulin to move sugar into the cells, directly targeting for insulin resistance. They lower the amount of sugar released by the liver and make fat cells more sensitive to the effects of insulin. Two major drugs of this class are included Actos (pioglitazone) and Avandia (rosiglitazone) [14,15]. Recently, Avandia looks to be prohibited from the EU market and heavily restricted here in the US and several Asian countries because several studies were reported the serious problems on heart failure.

Biguanides improve insulin's ability to move sugar into cells especially into the muscle cells. A biguanide class is included Metformin (Glucophage) which also improves control of glycemia primarily by inhibiting hepatic gluconeogenesis and glycogenolysis [17]. However, biguanides can cause very serious condition called lactic acidosis so this is primarily a concern in people with kidney problems or heart failure.

Alpha-glucosidase inhibitors retard the digestion and absorption of carbohydrates in the small intestine and hence reduce the increase in blood glucose level after meals. These drugs do not cause the pancreas to produce more insulin. However, side effects can be bloating, gas and diarrhea. Current prescribing drugs are Precose and Glyset [14,15].

Rosiglitazone (Avandia), pioglitazone (Actos) and metformin (Glucophage) act by both reducing glucose production in the liver, and increasing insulin dependent glucose uptake in muscle cells [14,15,17].

Mechanisms of banaba extract and corosolic acid

The blood sugar-lowering activity of extracts prepared from the leaves of banaba has been demonstrated in a number of animal models and clinical studies, including normal rats fed high levels of soluble starch [18], alloxan-diabetic rats [19,20], male genetically obese-diabetic (KK-Ay) mice [2]. Hypoglycemic effects of banaba extracts have also been shown in placebo-controlled clinical trials in subjects with type II diabetes [7] and mild type II diabetes [8]. Like antidiabetic drugs, several mechanisms of banaba and corosolic acid, one of components from banaba extracts on lowering blood glucose levels were elucidated [6].

(a) Glucose Transport Enhancers

Studies indicate that the majority of antidiabetic constituents so far identified in banaba are glucose transport enhancers [6,21,22]. These substances of great interest for their potential use as energy tonics for the elderly and as means to maintain healthy blood glucose [6]. The glucose transport-enhancing activity of banaba was previously shown in a group of ellagitannins in the leaves known as flosin B, lagerstroemin and reginin A [21,22]. Lagerstroemin produced dose-dependent glucose transport-activating activity from concentrations of 0.02 to 0.30mM [22], and in subsequent studies was shown to possess multiple insulin-like activities *in vitro* [21]. The results suggested that the "insulin-like" glucose transport-enhancing activity of "the ellagitannins or their metabolites" was responsible for the blood glucose-lowering activity of banaba reported in studies in diabetic patients [22].

(b) Insulin-Mimetic (peptide analogs) activity

More recently, it was shown that small molecule components of gallotannins, which along with ellagitannins are major components of tannic acid, not only hold dose-dependent glucose transport-stimulating activity in mouse pre-adiposcytes, but many of the insulin-mimetic activities found from banaba as well. These small components were identified as alpha- and beta-pentagalloylglucose (α- and β-PGG). However, of the two, the alpha form was clearly the more potent. α- PGG also stimulated translocation of GLUT4 [23], inhibited differentiation of pre-adipocytes, and targeted the insulin receptor, the latter helping to explain its various insulin-like activities.

(c) GLUT4 activation

GLUT4 is a protein in muscle and gat cells which transports glucose across plasma membrane, thereby allowing cells to gain energy and to maintain healthy blood sugar levels. Physical exercise is widely known to help maintain healthy glucose metabolism [24,25] in large part because physical exercise enhances GLUT4 levels in muscles. Indeed, a long-term high-fat diet has the opposite of lowering their levels [26] and whereas the increase in blood flow from exercise allows GLUT4 to move into muscle membranes [5,27].

(d) Alpha-Amylase and Alpha Glucosidase Inhibitors

One study found banaba tea inhibited α-amylase activity by 38% [26] and others have reported that methanol and water extracts of the leaves inhibit both α-amylase and α-glucosidase [18]. Both α-amylase and α-glucosidase are enzymes involved in the digestion of carbohydrates and allow the accompanying increase in blood glucose levels following a meal containing starches and sugars. By inhibiting these enzymes, carbohydrate absorption is delayed along with the increase in blood sugar.

Discussion

Diabetes is widely and seriously recognized as one of the leading causes of death and disability in the world. Diabetes often leads to blindness, heart and blood vessel disease, stroke, kidney failure, amputations, and nerve damage. Currently, several antidiabetic drugs have been prescribed for lowering blood sugar levels and for retarding further development. However, unfortunately, various adverse effects such as heart failure, hypoglycemia, kidney failure and weight gain are reported. After all, FDA recently warned those side effects and prohibited selling of Avandia in the US. Due to various reported side effects, many scientists have been seeking for the substitution as antidiabetic drugs from the nature which have a hypoglycemic effect [28]. Prior to the administration of nutraceuticals for antidibetes, however, it is necessary to understand their mechanism to be functioned correctly, comparing with that of current antidiabetic drugs.

All sulfonylurea drugs may cause hypoglycemia. Most patients become resistant to these drugs over time, and may require either dose adjustments or a switch to insulin [14,15,16]. The administration of oral hypoglycemic drugs has been associated with increased cardiovascular mortality as compared with treatment with diet alone or diet plus insulin.

Alpha-glucosidase inhibitors are generally well tolerated, and do not cause hypoglycemia [14,15]. The most common adverse effects are gastrointestinal problems, including flatulence, diarrhea, and abdominal pain.

Metformin causes gastrointestinal (stomach and digestive) reactions in about a third of patients. A rare, but very serious, reaction to metformin is lactic acidosis, which occurs in patients with multiple medical problems, including renal insufficiency [17].

Thiazolidinediones [17] are generally well tolerated in early trials, but they are structurally related to an earlier drug, troglitazone, which was associated with liver function problems. Research showed that after one to 16 months of therapy with pioglitazone or rosiglitazone, some patients developed serious edema and signs of congestive heart failure [11,13]. Due to various adverse effects from these antidiabetic drugs, most of researchers have been found the active component for diabetes from natural resources [28,29,30]. Among several plants, the most strong candidate was banaba and corosolic acid as ingredients. When we investigate each mechanism of antidiabetic drugs, several same mechanisms can meet with those of banaba leaf extracts.

Oral administration of corosolic acid (10 mg/kg) to male genetically type 2 diabetic (KK-Ay) mice produced a decrease in blood glucose levels which reached statistical significance only at 4 hours post-administration [6]. The antidiabetic activity of an extract from the leaves of *Lagerstroemia speciosa* has been demonstrated in a randomized clinical trial at daily dosages of 32 and 48mg (1% corosolic acid) for 2 weeks showed a significant reduction in the blood glucose levels [7].

If we look several mechanisms of banaba and corosolic acid closely, there are same mechanism with that of antidibetic drugs. One of isolated six pentacyclic triterpenes from banaba leaves, corosolic acid was shown the best bioactivity against alpha-glucosidase, contributes most to the alpha-glucosidase inhibitory activity [31] and banaba tea inhibited α-amylase activity by 38% [26]. With these results, banaba and corosolic acid can be replaced with Precose and Glyset as alpha-amylase and alpha-glucose inhibitors.

Miura *et al*.[6] reported that corosolic acid induces GLUT4 translocation onto plasma membrane. Binding of insulin to receptors on muscle cells leads rapidly to fusion of those vesicles with the plasma membrane and insertion of the glucose transporters (GLUT4), thereby giving the cell an ability to efficiently take up glucose. Thereby, banaba and corosolic acid make the induction of GLUT4 translocation and uptake of glucose into the cells, lowering glucose levels in the blood. Furthermore corosolic acid stimulates glucose uptake via enhancing insulin receptor phosphorylation [32]. This mechanism can be similarly functioned as pioglitazone (Actos) and rosiglitazone (Avandia) like insulin sensitizers were shown [14,15].

Fructose-2,6-bisphosphate (F-2,6-BP) plays a critical role in hepatic glucose output by regulating gluconeogenesis and glycolysis in the liver. Corosolic acid increased the production of F-2,6-BP along with a decrease in intracellular levels of cAMP both in the presence and in the absence of forskolin in isolated hepatocytes. Corosolic acid inhibits gluconeogenesis by increasing the production of F-2,6-BP by lowering the cAMP level and inhibiting PKA activity in isolated hepatocytes [33]. These effects on hepatic glucose metabolism may underlie the various antidiabetic actions of corosolic acid. Rosiglitazone (Avandia), pioglitazone (Actos) and metformin (Glucophage) were shown decreases hepatic glucose production so banaba and corosolic acid surely can be shown good efficacy instead of those current drugs [14,15,16].

Stimulation of insulin receptors is known to cause phophorylation of several proteins on tyrosine residues because this event is an essential for insulin's action on downstream signaling molecules. Hattori *et al*. [1] found that lagerstroemin induces tyrosine-phosphorylation of IRβ (insulin receptor). This can be proved that laberstroemin, one of extract fractions from banaba can be antidibetic drugs such as Metformin which activates directly insulin receptors.

Consequently, Banaba extract contains several bioactive components including corosolic acid and tannins, including lagerstroemin that act like insulin lowering the blood sugar in the body. Corosolic acid is a triterpenoid glycoside that improves the cellular uptake of glucose and thought to stimulate glucose uptake and have insulin-like activity [3]. This component was observed to be an activator of glucose transport into cells, which ultimately results in a lowering blood glucose levels. The latter activity is thought to be secondary to activation of the insulin receptor tyrosine kinase or the inhibition of tyrosine phosphatase. Transporting glucose into cells is critical for providing the energy necessary for those cells to carry out their vital functions.

With many published data, banaba and its extracts could be functioned on lowering or maintaining blood sugar levels with different mechanism. Banaba extracts may play a role in the treatment of diabetes, by affecting factors (such as blood glucose level) that are associated with the development of diabetes. It also significantly increased insulin sensitivity and GLUT4 translocation, improved hyperglycemia, lowered hepatic lipid contents and triglycerides. It also acts as alpha-glucosidase inhibitors, slowing down the absorption of starchy foods from the intestine, thereby retarding the rise in blood glucose after meals [34].

Unfortunately, there are no direct applications to evaluate the mechanism of banaba extract on human subjects, which can be limited to confirm the mechanism. However, there are several human studies with banaba extract [7,8,9,10], which were shown the hypoglycemic effects and safety for a short and long-term period. It is impossible to speculate the correct effective mechanism in the human body but the banaba extract surely could be functioned on lowering blood sugar level without adverse effects. Those functions and mechanisms of banaba extracts mean that banaba will be the best natural antidiabetic remedy for prevention and treatment of diabetes as natural gift without any other side-effects shown in current prescribed antidiabetic drugs. Therefore, banaba will be very promising candidate for future antidiabetic drug market as ingredients or themselves.

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