

GLUCOSE *Help*™

For Healthy Blood Glucose Levels

Lagerstroemia speciosa, L. Extract,
18% Corosolic Acid

OPTI  URE®
BRAND
CHEMCO INDUSTRIES INC.

GLUCO *Help*™

Metabolic Syndrome

Metabolic syndrome isn't a disease, but is related to a cluster of metabolic abnormalities which include high blood pressure, resistance to insulin, excess body weight (especially abdominal fat), abnormal cholesterol and triglyceride levels, and elevated inflammatory markers, such as C-reactive protein (CRP). Having at least three of these disorders increases the likelihood of developing diabetes, obesity, heart disease or stroke. Each disorder, in itself, is a risk factor for other diseases. In combination, though, these disorders dramatically boost the chances of developing life-threatening illnesses.

Metabolic syndrome is a serious, emerging health concern amongst the medical community. It's becoming more prevalent among American adults—as many as one in four are affected. Metabolic syndrome occurs when blood glucose levels are abnormally high. They are not high enough to be classified as diabetic, but are adequately elevated so that excess insulin in the blood increases the risk for other health consequences.

GlucoHelp™ is a beneficial nutraceutical for individuals who struggle with one of the facets of metabolic syndrome—insulin resistance. GlucoHelp™ activates facilitative glucose transporters, thereby decreasing the need for insulin secretion. It also maintains a slight lowering of blood sugar without causing hypoglycemia, even in healthy subjects with normal blood glucose levels. GlucoHelp™ is extracted from the leaves of *Lagerstroemia speciosa*, the botanical name for banaba. Banaba leaf extracts have a proven record of safety and efficacy for controlling blood glucose levels and may assist with overcoming insulin resistance.

The high content of corosolic acid (18%) in GlucoHelp™ is likely to increase its potency in maintaining healthy blood glucose levels.

Banaba's Active Compound—Corosolic Acid

GlucoHelp™ is a unique dietary ingredient which contains at least 18 percent of the bioactive substance found in banaba leaves, corosolic acid. Banaba, commonly known as Crepe Myrtle, grows widely in tropical areas, including the Philippines, India, and Southeast Asia. Banaba is a familiar plant that displays beautiful flowers mid-summer. Because of its graceful surface texture and pretty shape, the plant is sometimes referred to as Noble "Divine Flower."

The banaba tree grows from 5 to 20 meters in height, and the leaves are smooth, oblong, and 12 to 25 centimeters long. The flowers are purple or mauve-pink. Banaba can be found growing in Bataan, on the islands of northern Luzon and Palawan, and in the Sulu Archipelago. It is a popular folk medicine in Southeast Asia. In the Philippines, a tea brewed from banaba leaves is consumed as a beverage and is used as a folk medicine for the treatment of diabetes mellitus.

Researchers at the Hiroshima University School of Medicine in Japan and University of the Philippines tried to identify the active ingredient(s) in banaba. They isolated a triterpenoid compound, known as corosolic acid, from a methanol extract of banaba leaves as an activator of glucose uptake of Ehrlich tumor cells (Murakami C, et al. *Chem Pharm Bull* (Tokyo). 1993; 41:2129-2131). Corosolic acid is also present in other plants, including *Eriobotrya japonica*, *Rhabdosia japonicus*, *Epilobium angustifolium*, and *Elliottia paniculata* (Takayama, Hiromitsu, et al. US Patent Serial No. 866733).

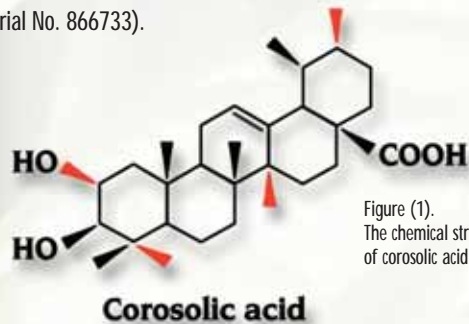


Figure (1).
The chemical structure
of corosolic acid

The hypoglycemic effect of corosolic acid has been confirmed by Tommasi and his coworkers in Japan. (Tommasi ND, et al. *Plant Med*. 1991; 57:414-416). They have isolated corosolic acid by methanol extraction of the leaves of *Eriobotrya japonica*, a small tree commonly known as "loquat," and studied its hypoglycemic effect in genetically diabetic mice. They found that corosolic acid produced a marked inhibition of glycosuria (the presence of glucose in the urine) in a dose-dependent manner. Figure 2 shows the effects of 1 mg, 10 mg, and 50 mg of corosolic acid per kg body weight on glycosuria. Corosolic acid showed a good inhibition of glycosuria at 4 and 7 hours with the three doses tested. The inhibitory effect was completely reverted only after 18-24 hours.

These findings suggest that the high content of corosolic acid (18%) in GlucoHelp™ is likely to increase its potency in maintaining healthy blood glucose levels. This prediction is also based on results obtained from a dose-dependent study of a 1% corosolic acid extract from banaba leaves sold by Soft Gel Technologies, Inc.® under the trade name GlucoTrim®.

In this clinical trial, subjects with Type II diabetes (non-insulin



Figure (2). Effect of different doses of corosolic acid on glycosuria in mice:
 ■ 50 mg/kg, ■ 10 mg/kg, □ 1 mg/kg.

dependent diabetes mellitus, NIDDM) received a daily oral dose (16, 32, and 48 mg) of GlucoTrim® (standardized to 1% corosolic acid) for 15 days at a time, followed by a 10-day washout period between the doses. Compared to the control, GlucoTrim® showed a drop in blood glucose levels over the dose range of 16-48 mg/day. This translates to a daily dose of 0.16-0.48 mg of corosolic acid, the active ingredient. A statistically significant reduction in blood glucose levels was observed at the 48 mg/day dose. These results clearly revealed that oral formulations of an extract from the leaves of *Lagerstroemia speciosa* exerted a marked lowering of blood sugar in Type II diabetics in a dose-dependent manner.

A Likely Mechanism of Action

Insulin resistance in peripheral tissues, together with the impairment of glucose-induced insulin secretion from pancreatic beta cells, is known as one of the major pathogenic factors of Type II diabetes. Insulin is a hormone produced by the pancreas that helps regulate the amount of sugar in the body. Normally, the digestive system breaks down some of the food into sugar (glucose). Then the body uses insulin to transport glucose into the cells, where it's converted to energy to fuel the body's processes.

In addition to glucose transport, insulin is intimately involved in adipogenesis, a process which involves proliferation of preadipocytes (pre-fat cells) and differentiation of preadipocytes into adipocytes (fat cells) with accumulation of fat in adipocytes. As a result of its adipogenic effect, insulin has the undesirable effect of promoting obesity in patients with Type II diabetes.

Unfortunately, some of the anti-diabetic drugs which are currently being used to stimulate insulin secretion in patients with Type II diabetes also possess adipogenic activity. Thus, while current drug therapy may provide a reduction in blood sugar, it often promotes obesity. Accordingly, new ingredients for treating hyperglycemia are desirable. Ingredients that stimulate glucose uptake without generating concomitant adipogenic side effects are especially desirable.

Interest has been generated in developing therapeutic agents that

directly increase muscle glucose transport. Glucose uptake across the plasma membrane is mediated by carrier proteins known as glucose transporters (GLUT). Skeletal muscles and adipocytes have been revealed to express glucose transporter GLUT4, and have the ability to move GLUT4 from intracellular pools to the plasma membrane. This translocation is stimulated by insulin. Defects in GLUT4 translocation contribute to characteristics of Type II diabetes. It is known that, in response to insulin secretion, GLUT4 undergoes translocation from a low-density microsomal membrane to the plasma membrane (PM) fraction permitting the entry of glucose into myocytes (muscle cells).

In a preliminary study, researchers in Japan examined the dose-dependent response (0.4, 2, 12 mg per kg) of corosolic acid on lowering blood glucose in genetically Type II diabetic mice (KK-Ay mice). They found that the most effective dose was 10 mg per kg body weight, which meant that they studied the effect of a glucose transporter of corosolic acid at this particular dosage. Corosolic acid increased the PM GLUT4 protein content of muscle in KK-Ay mice (Miura T, et al. *Biol Pharm Bull.* 2004; 27:1103-5). Single oral administration of corosolic acid (10 mg per kg body weight) to the diabetic mice reduced blood glucose when compared with the control group (Figure 3). Corosolic acid did not affect the plasma insulin over the period of 2 to 4 hours after administration in the diabetic mice. Corosolic acid administered to the diabetic mice also significantly increased facilitative glucose transporter isoform 4 (GLUT4) translocation from the low-density microsomal membrane to the plasma membrane (Figures 4 and 5) in muscle tissue. The relative amount of GLUT4 in the muscle plasma membrane fraction in the muscle from corosolic-treated mice was 148% of that observed in the control mice (Figure 5), but was not changed in the low density membrane fraction (Figure 4).

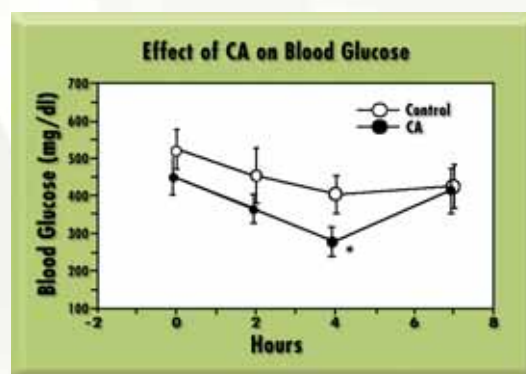


Figure (3). Effect of corosolic acid (CA) on blood glucose in KK-Ay Mice (low density membrane). Each value represents the mean \pm S.E.M. from 3-5 mice. Significantly different p. value, *P<0.05.

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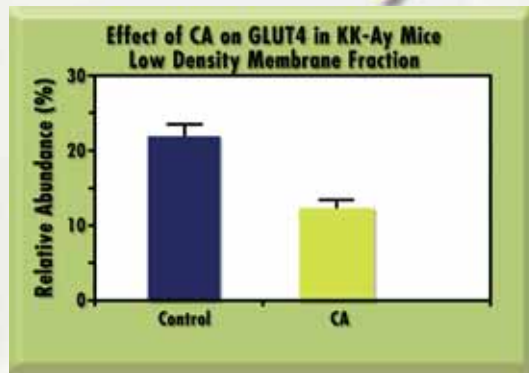


Figure (4). Effect of corosolic acid (CA) on GLUT4 protein content in KK-Ay Mice (low density membrane). Each value represents the mean \pm S.E.M. from 3-5 mice.

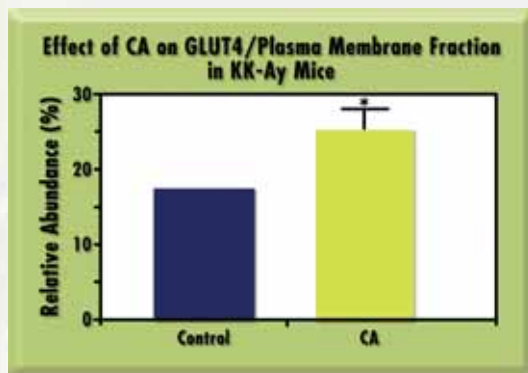


Figure (5). Effect of corosolic acid (CA) on GLUT4 protein content in KK-Ay Mice (plasma membrane). Each value represents the mean \pm S.E.M. from 3-5 mice. Significantly different from pre-value, * $p < 0.05$

These results suggest that the hypoglycemic effect of corosolic acid is derived, at least in part, from increased glucose transport, presumably because of the increase of GLUT4 translocation in total muscle membrane. These findings imply that GlucoHelp™, standardized to 18% corosolic acid, may help in regulating blood sugar within the normal range and may promote healthy weight management.

Research indicates that high-dose corosolic acid may increase the activity of facilitative glucose transporters, specifically GLUT4, which is located in fat tissue, heart and skeletal muscle. This carrier-mediated process leads to more efficient utilization of glucose and also induces a slight lowering of blood sugar without causing hypoglycemia. The need for insulin is reduced, since insulin is secreted in response to high blood glucose levels. When blood glucose is utilized as fuel for the body and brain and is not in excess, it does not get stored in adipose cells. It is likely that glucose and insulin level modulation reduces total caloric intake and encourages moderate weight loss.

As previously stated, insulin resistance is an impaired response to the body's own insulin resulting in active muscle cells not metabolizing glucose as easily as they should. It is one of the risk factors in metabolic syndrome. Existing pharmacotherapeutic agents for the treatment of insulin resistance and hyperinsulinemia cause significant negative side effects. Past research indicated that banaba leaf and its corosolic acid extracts demonstrated a high degree of safety, minimal side effects, and presented a unique therapeutic opportunity. Clearly, current research demonstrates that high-strength corosolic acid (18%) from banaba may offer significant advantages. GlucoHelp™ may benefit those trying to overcome insulin resistance by helping them utilize glucose more effectively.

References

- Murakami C, Myoga K, Kasai R, Ohtani K, Kurokawa T, Ishibashi S, Dayrit F, Padolina WG, Yamasaki K: Screening of plant constituents for effect on glucose transport activity in Ehrlich ascites tumour cells. *Chemical and Pharmaceutical Bulletin* (Tokyo) 1993; 41:2129-2131
- Tommasi ND, Simone FD, Cirino G, Cicara C, Pizza C. Hypoglycemic effects of sesquiterpene glycosides and polyhydroxylated triterpenoids of *Eriobotrya japonica*. *Planta Medica* 1991; 57:414-416
- Takayama, Hiromitsu, et al. US Patent Serial No. 866733
- Judy WV, Hari SP, Stogsdill WW, Judy JS, and Naguib YMA, Passwater R: Antidiabetic activity of a standardized extract (Glucosol®) from *Lagerstroemia speciosa*, leaves in Type II diabetics. A dose-dependence study. *Journal of Ethnopharmacology* 2003; 87:115-117
- Miura T, Itoh Y, Kaneko T, et al. Corosolic acid induces GLUT4 translocation in genetically type 2 diabetic mice. *Biological & Pharmaceutical Bulletin* 2004; 27:1103-5
- Kakuda T, Sakane I, Takihara T, Ozaki Y, Takeuchi H, Kuroyanagi M: Hypoglycemic effect of extracts from *Lagerstroemia speciosa* L. leaves in genetically diabetic KK-Ay mice. *Bioscience, Biotechnology, and Biochemistry* (Tokyo) 1996; 60:204-208
- Liu F, Kim J-K, Li Y, Liu X-q, Li J, Chen X: An extract of *Lagerstroemia speciosa* L. has insulin-like glucose uptake-stimulatory and adipocyte differentiation-inhibitory activities in 3T3-L1 cells. *Journal of Nutrition* 2001; 131: 2242-2247
- Suzuki Y, Unno T, Ushitani M, Hayashi K, Kakuda T: Antiobesity activity of extracts from *Lagerstroemia speciosa* L. leaves on female KK-Ay mice. *Journal of Nutritional Science and Vitaminology* (Tokyo) 1999; 45:791-795



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