GLUCOSE UPTAKE-STIMULATORY POTENTIAL OF COROSOLIC ACID: A MECHANISM BASED REVIEW

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ABSTRACT

Corosolic acid, (2 alphahydroxy ursolic acid, Glucosol) is a pentacyclic triterpenoid compound widely existing in many traditional Chinese medicinal herbs, has been proved to have anti diabetic effects on animal experiments and clinical trials. Corosolic acid which is structurally similar to ursolic acid. Corosolic acid is usually extracted from Banaba (Lagerstroemia speciosa) leaf. It is reported to exhibit antihyperlipidemic, antioxidant, anti-inflammatory, antifungal, antiviral, antineoplastic, osteoblastic and protein kinase C inhibition activity. Pure Corosolic acid has been reported to decrease blood sugar levels within 60 min in human subjects. The beneficial effects of banaba and Corosolic acid with respect to various aspects of glucose and lipid metabolism appear to involve multiple mechanisms, including enhanced cellular uptake of glucose, impaired hydrolysis of sucrose and starches, decreased gluconeogenesis and the regulation of lipid metabolism. Corosolic acid increased glucokinase activity without affecting glucose-6-phosphatase activity, suggesting an increase in glycolysis. Various studies indicated the pharmacological actions of corosolic acid are not summarized based on the mechanism of action. So in this review, our efforts have been devoted to provide some mechanism based anti diabetic potential of Corosolic acid which may prove as additional information and shall be helpful in future research.

INTRODUCTION

Corosolic acid (CRA) is a substance extracted from Chinese medicinal herbs, such as the *Lagerstroemia speciosa* L. (Banaba) belonging to family *Lythraceae* and has been reported to have biological activities as discovered in *in vitro* and experimental animal studies, particularly due to its influence on blood sugar (diabetes). It is found in many plants, particularly banaba, but also in almond hulls, *Weigela subsessilis*, *Perilla frutescens*, *Campsis grandiflora* and other herbs. Corosolic acid (CRA) has also been isolated from a number of other plant species including but not limited to *Vaccinium macrocarpon* (cranberry), *Ugni molinae*, *Eriobotrya japonica*, *Perilla frutescens*, *Weigela subsessilis*, *Glechoma longituba*, *Potentilla chinensis*, *Rubus biflorus*, and *Phlomis umbrosa*.[2] Miura and co-worker, have been reported to have anti-inflammatory and hypoglycemic activities. Corosolic acid (CRA) a constituent of banaba leaves. This pentacyclic triterpene inhibits glycogen phosphorylases. Chemically, Corosolic acid is a triterpenoid named 2α-hydric ursolic acid (Fig. 1), from banaba leave, *Tiarella polyphylla*, etc.[3, 4]

![Structure of Corosolic acid](image)

Fig. no.-1: Structure of Corosolic acid.

Recently, Corosolic acid has been reported to have anti diabetic activity in some animal experiments and clinical trials, suggested that the acute hypoglycemic effect of CRA is derived, at least in part, from an increase in GLUT4 translocation in mouse muscle, and that CRA improves glucose metabolism by reducing insulin resistance. Recently, Fukushima et al. [1] have shown that CRA has lowered post challenge plasma glucose levels in human. Many antidiabetes drugs now carry warning labels about their dangerous side effects, which can include an increased risk of heart failure. There's no question as to why so many people are searching for natural alternatives, like banaba leaf extract, that can help them manage blood sugar.[5]

Corosolic acid (CRA) can work like insulin to reduce blood sugar levels by transporting glucose into cells and out of the bloodstream. This can be beneficial to anyone who has trouble with high blood sugar, and especially to those with insulin resistance or diabetes.[6, 7] The antidiabetic effect of corosolic acid is well elaborated by different researchers but their mechanism of action is not clearly understood. In this review we put our efforts to provide some mechanism based anti diabetic effect of corosolic acid which will prove beneficial and shall pave the way for further research.

![General mechanism of action of insulin for glucose transport via GLUT 4](image)

Fig. no. 2: General mechanism of action of insulin for glucose transport via GLUT 4.
The above figure describes the general mechanism of action of insulin. Insulin binds with its specific receptors in turn causes activation of Insulin receptor substrate (IRS) which is a signalling adapter protein that in humans plays a key role in transmitting signals from the insulin and insulin receptors to intracellular pathways P13K/AKT (also known as Protein kinase B) and ErK (Extracellular signal-regulated kinases) MAP kinase (Mitogen-Activated Protein Kinases. The ERK/MAPK pathway is a chain of proteins in the cell that communicates a signal from a receptor on the surface of the cell to the DNA in the nucleus of the cell. Tyrosine phosphorylation of IRS-1 by insulin receptor (IR) introduces multiple binding sites for proteins bearing SH2 homology domain, such as PI3K. Which involved in interaction with IRS-1, produces PIP3, which, in turn, recruits Akt kinase and phosphorylation of Akt takes place. The cascade is followed by glucose uptake by GLUT4 which translocated from catalytic site and fixed with the membrane for glucose transport.

ANIMAL STUDIES:
Some studies reported that Corosolic acid reduced the blood glucose levels and significantly lowered plasma insulin levels in KK-Ay mice 2 weeks after a single oral dose of 2 mg/kg. Furthermore, blood glucose in KK-Ay mice treated with Corosolic acid significantly decreased in an insulin tolerance test. The muscle GLUT4 translocation from low-density microsomal membrane to plasma membrane was significantly increased in the orally Corosolic acid-treated mice when compared with that of the controls (P<0.05). Fukushima M et.al demonstrated that Corosolic acid has an effect on lowering post challenge plasma glucose levels in vivo in human. Subjects treated with Corosolic acid showed lower glucose levels from 60 min until 120 min and reached statistical significance at 90 min. Corosolic acid in the diet increased the expression of peroxisome proliferator-activated receptor-alpha (PPAR-α) in the liver and PPAR-γ in white adipose tissues, thus providing a mechanistic explanation for the loss in body weight and the decrease in hepatic steatosis in these mice. These results indicate that Corosolic acid may be beneficial in addressing various aspects of the metabolic syndrome that consists of hyperlipidemia, obesity, hypertension, and insulin resistance.

CLINICAL STUDIES:
The anti diabetic activity of a banaba extract standardized to 1% corosolic acid (Glucosol) has been demonstrated in a randomized clinical trial involving Type II diabetics. Subjects received a daily oral dose of Glucosol and blood glucose levels were measured. Glucosol at daily dosages of 32 and 48mg (0.32 and 0.48 mg Corosolic acid, respectively) for 2 weeks showed a significant reduction in the blood glucose levels. Glucosol in a soft gel capsule formulation showed a 30% decrease in blood glucose levels compared to a 20% drop seen with dry powder filled hard gelatin capsule formulation suggesting that the soft gel formulation has a better bioavailability than a dry powder formulation.

Corosolic acid is suggested to induce GLUT4 translocation (Fig.no.3). Translocation of more GLUT4 glucose transporters to the cell surface means increased insulin action. The action of insulin is mediated by tyrosine phosphorylation and initiated by the binding of insulin to the insulin receptor. Corosolic acid may act as an insulin sensitizer, enhancing insulin receptor B phosphorylation indirectly by inhibiting certain nonreceptor protein tyrosine phosphatases. Corosolic acid may also enhance GLUT4 glucose transporter processing of glucose uptake into muscle cells. Another study reported that Corosolic acid increases fructose 2, 6-bisphosphate production, which enhances phosphofructokinase activity and inhibits fructose-1, 6-bisphosphatase. As a result, Corosolic acid enhances glycolysis and inhibits gluconeogenesis thus favoring lactic acid production. In the presence of lactic acid, Corosolic acid markedly enhances fructose 2, 6-bisphosphate production and favors glycolysis.
Fig. no. 4: Mechanism for decrease gluconeogenesis and increase glycolysis.

The fig.4 indicates the glycolysis regulation in the liver. Fructose 2,6-biphosphate is formed from Fructose 6-phosphate and allosterically activates PFK-1 to increase its affinity for fructose6-phosphate. The aspects of metabolic syndrome which may be addressed by Corosolic acid include obesity, insulin resistance, and hypertriglyceridemia and hypercholesterolemia.[18] Corosolic acid (20–100 μm) in a dose-dependent manner decreased gluconeogenesis by increasing production of fructose-2,6 diphosphate by lowering cyclic AMP levels and inhibiting protein kinase A activity. In addition, Corosolic acid increased glucokinase activity without affecting glucose-6-phosphatase activity, suggesting an increase in glycolysis.[19] The results provide additional mechanistic information regarding the anti diabetic actions of Corosolic acid.[21,22]

CONCLUSION

Various studies indicated that Corosolic acid is beneficial in maintaining blood sugar levels and obesity. Furthermore, Corosolic acid exhibits anti-inflammatory, antihyperlipidemic, antioxidant, antiviral, antitumor and appetite suppressant promoting effects. Corosolic acid also works as “insulin sensitizer” that may activate the IRS and other adapter proteins intracellularly for transmitting the signals to PI3K/AKT as well as MAPK/ERK pathways. Activation of these proteins and intracellular cascades in turn causes translocation of GLUT4 there by glucose uptake takes place. In liver corosolic acid also promotes glycolysis and suppresses gluconeogenesis there by proves as having antidiabetic potential. Extensive study about corosolic acid along with other drugs is required which may provide some research based evidence for synergistic effect of that combination therapy.

REFERENCES