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Glucose Uptake Rate of Insulin-Resistant Human Liver Carcinoma Cells (IR/HepG2) by Flavonoids from Enicostema littorale via IR/IRS1/AKT Pathway

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Abstract : Diabetes mellitus is a chronic metabolic disorder which will be the 7th leading cause of death by 2030. The current line of treatment for the diabetes mellitus is oral antidiabetic drugs (biguanides, sulfonylureas, meglitinides, thiazolidinediones and alpha-glycosidase inhibitors) and insulin therapy depending upon the type 1 or type 2 diabetes mellitus. But, these treatments have their disadvantages, ranging from the developing of resistance to the drugs and adverse effects caused by them. Alternative to these synthetic agents, natural products provides a new insight for the development of more efficient and safe drugs due to their therapeutic values. Enicostema littorale blume (A. Raynal) is a traditional Indian plant belongs to the Gentianaceae family. It is widely distributed in Asia, Africa, and South America. There are few reports on Swrtiamarin, major component of this plant for its antidiabetic activity. However, the antidiabetic activity of flavonoids from E. littorale and their mechanism of action have not yet been elucidated. Flavonoids have a positive relationship with disease prevention and can act on various molecular targets and regulate different signaling pathways in pancreatic β-cells, adipocytes, hepatocytes and skeletal myofibers. They may exert beneficial effects in diabetes by (i) improving hyperglycemia through regulation of glucose metabolism in hepatocytes; (ii) enhancing insulin secretion and reducing apoptosis and promoting proliferation of pancreatic β-cells; (iii) increasing glucose uptake in hepatocytes, skeletal muscle and white adipose tissue (iv) reducing insulin resistance, inflammation and oxidative stress. Therefore, we have isolated four flavonoid rich fractions, Fraction A (FA), Fraction B (FB), Fraction C (FC), Fraction D (FD) from crude alcoholic hot (AH) extract from E. littorale, identified by LC/MS. Total eight flavonoids were identified on the basis of fragmentation pattern. Flavonoid FA showed the presence of swertisin, isovitexin, and saponarin; FB showed genkwanin, quercetin, isovitexin, FC showed apigenin, swertisin, quercetin, 5-O-glucosylswertisin and 5-O-glucosylisoswertisin whereas FD showed the presence of swertisin. Further, these fractions were assessed for their antidiabetic activity on stimulating glucose uptake in insulin-resistant HepG2 cell line model (IR/HepG2). The results showed that FD containing C-glycoside Swertisin has significantly increased the glucose uptake rate of IR/HepG2 cells at the concentration of 10 µg/ml as compared to positive control Metformin (0.5mM) which was determined by glucose oxidase-peroxidase method. It has been reported that enhancement of glucose uptake of cells occurs due the translocation of Glut4 vesicles to cell membrane through IR/IRS1/AKT pathway. Therefore, we have studied expressions of three genes IRS1, AKT and Glut4 by real-time PCR to evaluate whether they follow the same pathway or not. It was seen that the glucose uptake rate has increased in FD treated IR/HepG2 cells due to the activation of insulin receptor substrate-1 (IRS1) followed by protein kinase B (AKT) through phosphoinositide 3-kinase (PI3K) leading to translocation of Glut 4 vesicles to cell membrane, thereby enhancing glucose uptake and insulin sensitivity of insulin resistant HepG2 cells. Hence, the up-regulation indicated the mechanism of action through which FD (Swertisin) acts as antidiabetic candidate in the treatment of type 2 diabetes mellitus.

Keywords : E. littorale, glucose transporter, glucose uptake rate, insulin resistance
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