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The present investigation evaluates the effectiveness of extract and its different fractions derived from *Helicteres isora* roots and the antidiabetic compounds derived from active fraction based on the activity guided phytopharmacological studies on high fat diet and low dose streptozotocin-induced type 2 Diabetes mellitus (HFD-STZ diabetic rats) and streptozotocin (STZ)-induced type 1 diabetic rats. The active constituents were isolated and identified as saponins from the n-butanol fraction. Treatment with the methanol extract, n-butanol fraction and isolated saponins of *H. isora* produced a significant reduction in elevated levels of glucose and lipids in experimental models of type 1 and type 2 Diabetes mellitus.

The isolated saponins were further evaluated for effects on glucose and lipid metabolism regulating genes in the liver and the adipose tissue of C57BL/KsJ-db/db mice by quantitative real time polymerase chain reaction (qRT-PCR) and reverse transcription polymerase chain reaction (RT-PCR). In type-2 diabetic C57BL/KsJ-db/db mice, the treatment caused a significant reduction in the serum lipid and glucose levels and increased the expression of adipisin, acyl coenzyme-A oxidase (ACOX), peroxisome proliferator activated receptor gamma (PPAR γ) and glucose transporter 4 (Glut4) while reduced expression of fatty acid binding protein 4 (FABP4) and glucose-6- phosphatase (G6Pase), whereas there was no effect on the expression levels of adiponectin, lipoprotein lipase (LPL), phosphoenol pyruvate carboxy kinase (PEPCK), glucose transporter 2 (Glut2), PPAR α, angiopecitin like 3 (ANGPTL3) and angiopecitin like 4 (ANGPTL4).
Based on the results of the in-vivo studies, further in-vitro studies were carried on to evaluate effects on PI3K/AKT pathway, AMPK pathway, glucose transporters and PPAR γ in an attempt to investigate mechanism of action of saponins and sapogenin at molecular level on C2C12 skeletal muscle cells and HepG2 hepatocytes. Incubation with saponins (100μg/ml) and sapogenin (100μg/ml) induced the phosphorylation of PI3K and the downstream target phospho-Akt (Ser473) relative to the PI3K total protein and Akt total protein levels respectively, in a time dependent manner while there was no phosphorylation of AMPK (Thr172) at any time point indicating no effect on AMPK pathway. There was increase in the Glut4 protein levels at 48 h incubation in the C2C12 skeletal muscle cells. Also, there was increase in the phospho-GSK-3α/β (Ser21/9) in a time dependent manner relative to the GSK3-β total protein. The results of the immunofluorescence study on C2C12 myotubes indicate the activation of phospho-Akt (Ser473) and translocation of glucose transporter Glut4 to the myotube cell membrane from the inner cytosolic compartment, in a time dependent manner.

The mechanism(s) of action of the active constituents saponins and the extract of H. isora could be stimulation of glucose transport to skeletal muscle and liver cells by activating PI3K/AKT pathway, regulation of glycogen synthesis through phosphorylation and inactivation of GSK-3α and β (downstream of Akt), inhibition of the enzyme glucose-6-phosphatase (G6Pase) in the liver which plays a critical role in blood glucose homeostasis (by catalyzing final step of gluconeogenesis and glycolysis), reduced expression of FABP4 in the adipose tissue and increased expression of insulin responsive glucose transporter Glut4 in adipose tissue and skeletal muscle cells.

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