ABSTRACT

Obesity owning to its strong association with high incidence of type 2 diabetes is one of the leading health disorders globally. Diabetes covers over 6% of the total world population and is a major concern in today's health care. The manifestation of type 2 diabetes from the prediabetic state is characterized by insulin resistance and thereafter inadequate insulin secretion that results in hyperglycemia and hyperlipidemia. Obesity associated type 2 diabetic patients have high chances for cardiovascular risks. Hence, there is a demand for early diagnosis and effective treatment of diabetes to prevent such complications. Since commercially available antidiabetic drugs fail to meet the demand, there is a need for exploring natural sources as an alternative strategy to treat diabetes that might be effective and economical.

This study mainly focuses on demonstrating the role of Naringenin (NG), a major flavanone in citrus fruits, as a natural antihyperglycemic agent and the mechanism by which NG exerts its action on high fat diet (HFD) fed streptozotocin (STZ) induced diabetic rats. After 6 weeks of dietary manipulation with HFD, rats were made diabetic by administering STZ (40 mg/kg b.wt.) intraperitoneally which represented the pathogenesis of type 2 diabetes in human. Treatment of diabetic rats with NG (25 mg/kg bw.) for 45 days markedly reduced hyperinsulinemia, improved glycogen content, restored lipid profile changes, decreased lipid peroxidation on the membrane; enhanced the activities of antioxidants and improved the levels of hepatic and renal function markers.

The mechanism by which NG exhibited antihyperglycemic effect was evaluated by studying the expression of marker proteins including Phosphatidylinositol-3-kinase (PI3k), phosphorylated Akt (p-Akt) and glucose transporter-4 (GLUT-4) involved in insulin signaling pathway and also its associated nuclear receptor protein peroxisome proliferator-activated receptors-γ (PPAR-γ) and inflammatory marker tumour necrosis factor-α (TNF-α) that contributes to insulin resistance. NG enhanced insulin stimulated glucose uptake via PI3k/Akt dependent GLUT-4 translocation and also modulated lipid and glucose metabolism by up-regulating PPAR-γ and down-regulating TNF-α.

Since postprandial hyperglycemia is one of the earliest abnormalities associated with type 2 diabetes, NG was checked for its potent inhibitory role against α-glucosidase activity *in vitro* and *in vivo*. It showed competitive inhibition towards mammalian α -glucosidase enzyme *in vitro* thereby competing with α-limit dextrins and oligosaccharide residues for binding to active site. Similar results have been obtained from molecular docking analysis, where NG showed preferential binding to active sites of human intestinal α -glucosidase enzymes. NG (25 mg/kg b.wt.) inhibited intestinal α-glucosidase activity *in vivo* by lowering the elevated postprandial blood glucose levels.