Preventive effect of curcumin on fructose diet induced insulin resistance in rats

Abstract

Insulin resistance (IR), a metabolic syndrome, has become a major public health concern worldwide. IR is a multi-factorial metabolic syndrome which includes hyperglycemia, hyperinsulinemia, dyslipidemia and hypertension and plays a major role in the development of Diabetes Mellitus (DM). The reason for the rapid development of DM may be due to change of lifestyle, dietary pattern and lack of physical activity with increased consumption of high sugar diet especially fructose. High fructose diet mediates oxidative stress which breeds IR leading to the pathogenesis of DM and its clinical manifestations. There are several therapeutic strategies in practice for the management of DM, but there are certain limitations due to their high cost and adverse side effects. The World Health Organization (WHO) expert committee on diabetes has recommended the use of natural plant medicine for the prevention / treatment of DM because of the likelihood of high compliance and become largely free from adverse effects. Many antidiabetic compounds have been studied and one such natural compound is curcumin, a polyphenol, found in turmeric (Curcuma longa from Zingerferezae family) which possesses a variety of biochemical and pharmacological effects. On this basis, the present study was focused to evaluate the effect of oral administration of curcumin against high fructose diet-fed model of IR on biochemical and oxidative stress parameters, their association with potential changes at metabolic and molecular level, and multivariate analysis to determine the most contributing factors in adult male Wistar rats. Rats were fed with high fructose diet (Group 2) to induce diabetes and curcumin was co-administered orally (Group 4) for a minimum period of eight weeks. In group 2 rats, the level of creatinine, glucose, insulin, low density lipoprotein (LDL),
total cholesterol (TC), triglyceride (TG), urea, uric acid, very low density lipoprotein (VLDL), nitric oxide (NO) were significantly \( p<0.05 \) increased and the level of albumin, high density lipoprotein (HDL) and total protein were observed to be decreased significantly \( p<0.05 \) when compared with group 1 control rats. The analysis of liver and kidney tissue homogenate showed a significant \( p<0.05 \) decrease in antioxidants such as catalase (CAT), glutathione peroxidase (GPx), glutathione reductase (GSH), superoxide dismutase (SOD), vitamin C and E, hexokinase and a significant \( p<0.05 \) increase in glucose-6-phosphatase and fructose-1, 6-bisphosphatase, lipid peroxides such as hydroperoxides and TBARS were observed in group 2 rats. These metabolic alterations with high fructose diet (Group 2) were significantly \( p\leq0.05 \) improved in rats co-administrated with curcumin (Group 4). Docking study was carried out to determine the binding efficiency of curcumin as agonist of PPAR\( \gamma \) which shows high affinity towards the receptor. Gene expression studies revealed that Endothelin-1 (ET-1), Peroxisome proliferator-activated receptor gamma coactivator-1\( \alpha \) (PGC-1\( \alpha \)), Pancreatic duodenal homeobox-1 (PDX-1), Forkhead Box containing protein-O (FOXO) genes influence IR through alteration of metabolic enzymes in group 2 and group 4 rats. With this observation, it is evident that the interaction of PPAR\( \gamma \) increases insulin sensitivity which regulates the transcription of genes that are associated with DM. Histological analysis of liver and kidney also revealed that the co-administration of curcumin protects the organs from the abnormal changes caused by the high fructose diet. Overall, these results suggest that the co-administration of curcumin along with fructose effectively prevents the metabolic abnormalities and oxidative stress in high fructose diet-induced IR in rats.

**Key words:** Insulin resistance, Diabetes mellitus, Hyperglycemia, Curcumin, High fructose diet, PPAR\( \gamma \), Antioxidant, ET-1, FOXO, PDX-1, PGC 1\( \alpha \).