ABSTRACT

Management of metabolic disorders places a heavy burden on healthcare systems globally. Dietary manipulations during developmentally plastic periods including the early postnatal phase can result in long-term beneficial or adverse health outcomes. Consumption of high-fructose diets early in life increases the risk of developing metabolic syndrome and associated cardiovascular and renal complications. Zingerone, a phytochemical mainly isolated from ginger (*Zingiber officinale)*, has been demonstrated to attenuate metabolic derangements in adult rats. The potential preventive effects of zingerone administered orally to neonatal male and female rats against the long-term development of high-fructose diet-induced metabolic derangements were investigated.

Four-day old male and female Sprague Dawley rat pups (n = 79) were randomly grouped and gavaged with: 10 ml/kg body weight of distilled water (W), 10 ml/kg body weight 20% fructose solution (FS), 10 ml/kg body weight fructose solution + 40 mg/kg body weight of zingerone in distilled water (ZF), or 40 mg/kg body weight of zingerone in distilled water (ZW) pre-weaning. After weaning, W and ZW continued on unlimited tap water while FS and ZF continued on unlimited fructose solution for 10 weeks. Commercial rat feed was provided *ad libitum*. Food and fluid intake was evaluated. Blood samples were collected for metabolic assays and assessment of general health markers. Growth performance, adiposity, hepatic lipid accumulation, renal function pathology and gastro-intestinal tract (GIT) organs' morphometry were assessed. Liver and kidney tissues were collected for histological evaluation.

Food intake was decreased; overall caloric intake was increased due to fructose feeding in both sexes ($P < 0.05$; ANOVA). When compared with the negative controls, the high-fructose diet significantly raised the terminal body masses [Females ($P < 0.0001$; ANOVA)], body mass index (BMI) [Females ($P = 0.0036$; ANOVA)], concentrations of triglycerides, total cholesterol, low density lipoprotein cholesterol, triglycerides to high density lipoprotein cholesterol ratio, visceral fat mass relative to body weight [Both sexes ($P < 0.05$; ANOVA)] and empty carcass mass [Females ($P = 0.0025$; ANOVA)]. Neonatally administered zingerone prevented ($P < 0.05$; ANOVA) the fructose-induced increase in body mass and empty carcass mass (Females), and hypercholesterolemia (Both sexes). Lee index and glycaemic parameters were not affected by the interventions in both sexes ($P > 0.05$; ANOVA).

Rats on the high-fructose diet compared to the negative controls had significantly increased hepatic lipid content [(%), $P = 0.0002$ (Males), $P < 0.0001$ (Females); ANOVA] and hepatic steatosis score [(%), $P = 0.0018$ (Males), $P < 0.0022$ (Females); Kruskal-Wallis ANOVA]. Zingerone administered neonatally prevented ($P < 0.05$; Kruskal-Wallis ANOVA) the fructose-induced increase in hepatic steatosis in both sexes. The plasma levels of uric acid, markers of liver function, lipid peroxidation and inflammation were not different ($P > 0.05$; ANOVA) across the different treatment groups in both sexes.

The group administered fructose only had significantly [$P = 0.0054$ (Males), $P = 0.0002$ (Females); ANOVA] increased levels of kidney injury molecule 1 (KIM-1), and decreased urinary space area [$P = 0.0001$ (Males), $P = 0.0016$ (Females); ANOVA] compared to the controls. Neonatally administered zingerone prevented the fructose-induced increase in the levels of KIM-1 [$P = 0.9262$ (Males), $P = 0.6667$ (Females); ANOVA], and fructose-induced reduction in the urinary space area [$P = 0.1505$ (Males), $P = 0.8265$ (Females); ANOVA] when the combined fructose and zingerone administered group was compared with the negative controls.

Sex related differences were observed in food, fluid and caloric intake, terminal mass, BMI, cholesterol subtypes, visceral fat percentage, GIT visceral organs and long bones' morphometry and empty carcass mass ($P < 0.05$; ANOVA).

In rats, zingerone can be used strategically in the neonatal phase for prophylactic management of long-term high-fructose diet-induced metabolic syndrome, non-alcoholic fatty liver disease and nephropathy. Future studies in human clinical trials should be undertaken to explore the applicability of these findings to reduce the burden of metabolic disease on healthcare systems.