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Effects of Delphinidin on Lipid Metabolism in HepG2 Cells and Diet-Induced Obese Mice

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Abstract : Non-alcoholic fatty liver disease (NAFLD) is characterized by an excess of hepatic lipids, and it is to author's best knowledge, the most prevalent chronic liver disorder. Anthocyanin-rich food consumption is linked to health benefits in metabolic disorders associated with obesity and NAFLD, although the precise functional role of anthocyanidin delphinidin (Dp) has yet to be established. The aim of this study was to investigate the effect of the Dp in NAFLD metabolic alterations by evaluating prevention or amelioration of hepatic lipid accumulation, as well as molecular mechanisms in two experimental obesity-related models of NALFD. In vitro: HepG2 cells were incubated with sodium palmitate (PA, 1 mM) to induce lipotoxic damage, and concomitantly treated with Dp (180 uM) for 24 h. Subsequently, total lipid accumulation was measured by colorimetric staining with Oil Red O, and total intrahepatic triglycerides were determined by an enzymatic assay. To assess molecular mechanisms, cells were pre-treated with PA for 24 h and then exposed to Dp for 1 h. In vivo: four-week-old male C57BL/6Nhsd mice were allocated in two main groups. Mice were fed with standard diet (control) or high-fat and high-carbohydrate diet (45% fat, HFD) for 16 wk to induce NAFLD. Then HFD was divided into subgroups: one treated orally with Dp (15 mg/kg bw, HFD-Dp) every day for 4 wk, while HFD group treated with vehicle (DMSO). Weight and fasting glucose were recorded weekly, while dietary ingestion was measured daily. Insulin tolerance test was performed at the end of treatment. Liver histology was evaluated with H&E and Masson's trichrome stain. RT-PCR was used to evaluate gene expression and Western Blot to determine levels of protein in both experimental models. Parametric data were analyzed with one-way ANOVA and Tukey's post-hoc test. Kruskal-Wallis and Mann-Whitney U test for non-parametric data, and $P < 0.5$ were considered significant. Dp prevented hepatic lipid accumulation by PA in HepG2 hepatocytes. Furthermore, Dp down-regulated gene expression of SREBP1c, FAS, and CPT1a without modifying AMPK phosphorylation levels. In vivo, Dp oral administration did not ameliorate lipid metabolic alterations raised by HFD. Adiposity, dietary ingestion, fasting glucose, and insulin sensitivity after Dp treatment remained similar to HFD group. Histological analysis showed hepatic damage in HFD groups and no differences between HFD and HFD-Dp groups were found. Hepatic gene expression of ACC and FAS were not altered by HFD. SREBP1c was similar in both HFD and HFD-Dp groups. No significant changes were observed in SREBP1c, ACC, and FAS adipose tissue gene expression by HFD or Dp treatment. Additionally, immunoblotting analysis revealed no changes in pathway SIRT1-LKB-AMPK and PPAR alpha by both HFD groups compared to control. In conclusion, the antioxidant Dp may provoke beneficial effects in the prevention of hepatic lipid accumulation. Nevertheless, the oral dose administrated in mice that simulated the total intake of anthocyanins consumed daily by humans has no effect as a treatment on hepatic lipid metabolic alterations and histological abnormalities associated with exposure to chronic HFD. A healthy lifestyle with regular intake of antioxidants such as anthocyanins may prevent metabolic alterations in NAFLD.

Keywords : anthocyanins, antioxidants, delphinidin, non-alcoholic fatty liver disease, obesity
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