Hepatoprotective effects of geniposide in a rat model of nonalcoholic steatohepatitis

Taotao Ma\textsuperscript{a}, Cheng Huang\textsuperscript{a}, Guojun Zong\textsuperscript{b}, Dajun Zha\textsuperscript{b}, Xiaoming Meng\textsuperscript{c}, Jun Li\textsuperscript{a} and Wenjian Tang\textsuperscript{a}

\textsuperscript{a}Department of Pharmacy, Anhui Medical University, Hefei, \textsuperscript{b}Hefei XinFeng Co. Ltd, Hefei and \textsuperscript{c}Department of Medicine and Therapeutics and Li Ka Shing Institute of Health Sciences, The Chinese University of Hong Kong, Hong Kong SAR, China

Abstract

Objectives  Nonalcoholic steatohepatitis (NASH), a metabolic disorder of the liver, may gradually evolve into fibrosis or cirrhosis. Recent studies have suggested that geniposide can effectively inhibit experimental liver fibrosis. Therefore, the aim of this study was to determine whether geniposide can influence the early phase of fibrogenesis in an animal model of NASH.

Methods  Male Sprague–Dawley rats were given a high fat diet alone or the same diet combined with geniposide at doses of 25, 50 or 100 mg/kg for six weeks. Ten rats received corresponding solvent as a normal control.

Key findings  Treatment with geniposide could improve liver histology through reducing the elevated liver index (liver weight/body weight), serum alanine aminotransferase and aspartate aminotransferase. Total cholesterol, triglycerides and free fatty acids in serum and liver decreased in geniposide-treated rats. Furthermore, geniposide increased serum insulin levels but reduced serum tumour necrosis factor-\textgreek{a} level in high-fat diet rats. In addition, geniposide suppressed expression of CYP2E1 and increased peroxisome proliferator-activated receptor-\textgreek{a} (PPAR\textgreek{a}) expression. These benefits may be associated with increased superoxide dismutase and decreased malondialdehyde in liver.

Conclusions  Geniposide exerts protective effects against hepatic steatosis in rats fed with a high fat diet; the underlying mechanism may be associated with its antioxidant actions or regulation of adipocytokine release and expression of PPAR\textgreek{a}.

Keywords  geniposide; lipid peroxidation; non-alcoholic steatohepatitis (NASH); rats

Introduction

With increased aging and weight-gain in our population, obesity and diabetes have become frequently associated with non-alcoholic fatty liver disease (NAFLD). NAFLD involves a wide spectrum of liver disease, ranging from simple steatosis to steatohepatitis and cirrhosis.\textsuperscript{[1–3]} Non-alcoholic steatohepatitis (NASH) forms the borderline between a benign condition (steatosis) and a serious/morbid condition (cirrhosis).\textsuperscript{[4]} Although the exact pathogenesis of NASH is yet to be understood, several studies have focused on strongly related markers, such as lipid peroxidation, reactive oxygen species (ROS) production, secretion of inflammatory cytokines and collagen deposition, to confirm the diagnosis of NASH or to develop new treatment strategies.\textsuperscript{[5]} Among these strategies, the use of complementary and alternative medicines, such as natural antioxidants and hepatoprotective plant products, has been popular in the last decade.\textsuperscript{[6]}

Geniposide is an iridoid glucoside extracted from \textit{Gardenia jasminoides} Ellis. Fruits, which have been used as a herbal medicine to treat liver and gall bladder disorders, such as hepatitis and acute jaundice, as well as inflammation and fever, in Chinese medicine for many years.\textsuperscript{[7–9]} A clinical study has shown that crude \textit{Gardenia} extract rapidly lowers serum bilirubin and transaminase levels in jaundice-induced acute hepatitis. A recent pilot study has also illustrated the effectiveness of geniposide in reducing insulin resistance and plasma markers of liver fibrosis in patients with NAFLD.\textsuperscript{[10,11]} However, no detailed analysis of the beneficial effect and mode of action of geniposide has ever been reported in the context of NASH. Thus, this study was conducted with the objective of evaluating the efficacy of the geniposide in protecting the liver against diet-induced NASH in rats.