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Original article

Kukoamine A attenuates insulin resistance and fatty liver through downregulation of Srebp-1c

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ABSTRACT

Nonalcoholic fatty liver disease (NAFLD) refers to a pathological condition of hepatic steatosis. Insulin resistance is believed to be the key mechanism mediating initial accumulation of fat in the liver, resulting in hepatic steatosis. Kukoamine A (KuA), a spermine alkaloid, is a major bioactive component extracted from the root barks of *Lycium chinense* (L. chinense) Miller. In the current study, we aimed to explore the possible effect of KuA on insulin resistance and fatty liver. We showed that KuA significantly inhibited the increase of fasting blood glucose level and insulin level, and the glucose levels in response to glucose and insulin load in HFD-fed mice, which was in a dose-dependent manner. KuA dose-dependently decreased the histological injury of liver, levels of hepatic triglyceride (TG), and serum AST and ALT activities in HFD-fed mice. The increase of serum levels of TNFα, IL-1β, IL-6 and C reactive protein in HFD-fed mice was inhibited by KuA. HFD feeding-induced increase of hepatic expression of Srebp-1c and its target genes, including fatty acid synthase (FAS) and acetyl CoA carboxylase 1 (ACC1), was significantly inhibited by KuA. Moreover, upregulation of Srebp-1c notably inhibited KuA-induced improvement of insulin-stimulated glucose uptake, decrease of lipid accumulation and H_2O_2 level in palmitic acid-treated AML-12 cells. In conclusion, we reported that KuA inhibited Srebp-1c and downstream genes expression and resulted in inhibition of lipid accumulation, inflammation, insulin resistance and oxidative stress. Overall, our results provide a better understanding of the pharmacological activities of KuA against insulin resistance and hepatic steatosis.

1. Introduction

Nonalcoholic fatty liver disease (NAFLD) refers to a pathological condition of hepatic steatosis that is not caused by excess alcohol consumption [1]. NAFLD has become a serious medical problem, influencing approximately 20%–40% of the people in different countries [2]. If not well-controlled, NAFLD ranges from hepatic steatosis to nonalcoholic steatohepatitis (NASH), cirrhosis, or hepatocellular carcinoma [3].

Although the mechanism of NAFLD is not clear, several factors including lipid metabolic disturbance and insulin resistance are closely associated with the occurrence and aggregation of NAFLD [4]. It is considered that insulin resistance and lipid dysregulation are original risk factors for NAFLD [5]. Insulin resistance is believed to be the key mechanism mediating initial accumulation of fat in the liver, resulting in hepatic steatosis [6]. Insulin resistance is associated with an increase in both synthesis of triglycerides, peripheral lipolysis, and oxidative stress, which are characteristics of fatty liver [7]. Thus, exploration of treating option of insulin resistance and hepatic steatosis is extremely important for the early attenuation of NAFLD. Most of the drugs for treating NAFLD have some adverse effects or contraindications [8]. In the last decades, naturally occurring substances have attracted much attention in the exploration of novel treatments for metabolic diseases [9–13]. Preclinical studies and clinical trials suggest the potential use of herbal derivatives in treating NAFLD, such as resveratrol [14], garlic [15], green tea [16], and coffee [17].

Abbreviation: ACC1, acetyl CoA carboxylase 1; CRP, C reactive protein; FAS, fatty acid synthase; H_2O_2, hydrogen peroxide; HFD, high fat diet; IL-1β, interleukin-1; IPGTT, intraperitoneal glucose tolerance test; IPITT, intraperitoneal insulin tolerance test; KuA, Kukoamine A; MDA, malondialdehyde; NAFLD, nonalcoholic fatty liver disease; PA, palmitic acid; Srebp-1c, sterol regulatory element binding proteins-1c; TG, triglyceride; TNFα, tumor necrosis factor α.

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Kukoamine A (KuA), a spermine alkaloid, is a major bioactive component extracted from the root barks of *Lycium chinense* (L. chinense) Miller. KuA possesses series of pharmacological effects, such as antihypertensive, anti-inflammatory, anti-analgesic, anti-sepsis, autoimmune-enhancing and neuroprotective activities [18]. Especially, KuA was proved to exhibit potent antioxidant activities. KuA could significantly attenuate H_2O_2-induced SH-SY5Y cell apoptosis via inhibition of oxidative stress and inactivation of the apoptotic pathway [19]. KuA could also prevent H_2O_2-induced toxicity in primary cerebellar granule neurons through anti-apoptotic and antioxidant activities [20]. However, whether KuA plays a protective role against hepatic steatosis and insulin resistance is unknown.

In the current study, we investigated the effect of KuA on insulin resistance and fatty liver in high fat diet (HFD)-treated mice and examined the effect of KuA on palmitic acid (PA)-induced insulin resistance and lipid accumulation in AML-12 cells. We showed that KuA attenuated insulin resistance and lipid accumulation in vivo and in vitro through downregulation of sterol regulatory element binding proteins-1c (Srebp-1c).

2. Materials and methods

2.1. Animal treatment

Animal treatment was approved by Animal Care and Use Committee of the First Affiliated Hospital of Xinxiang Medical

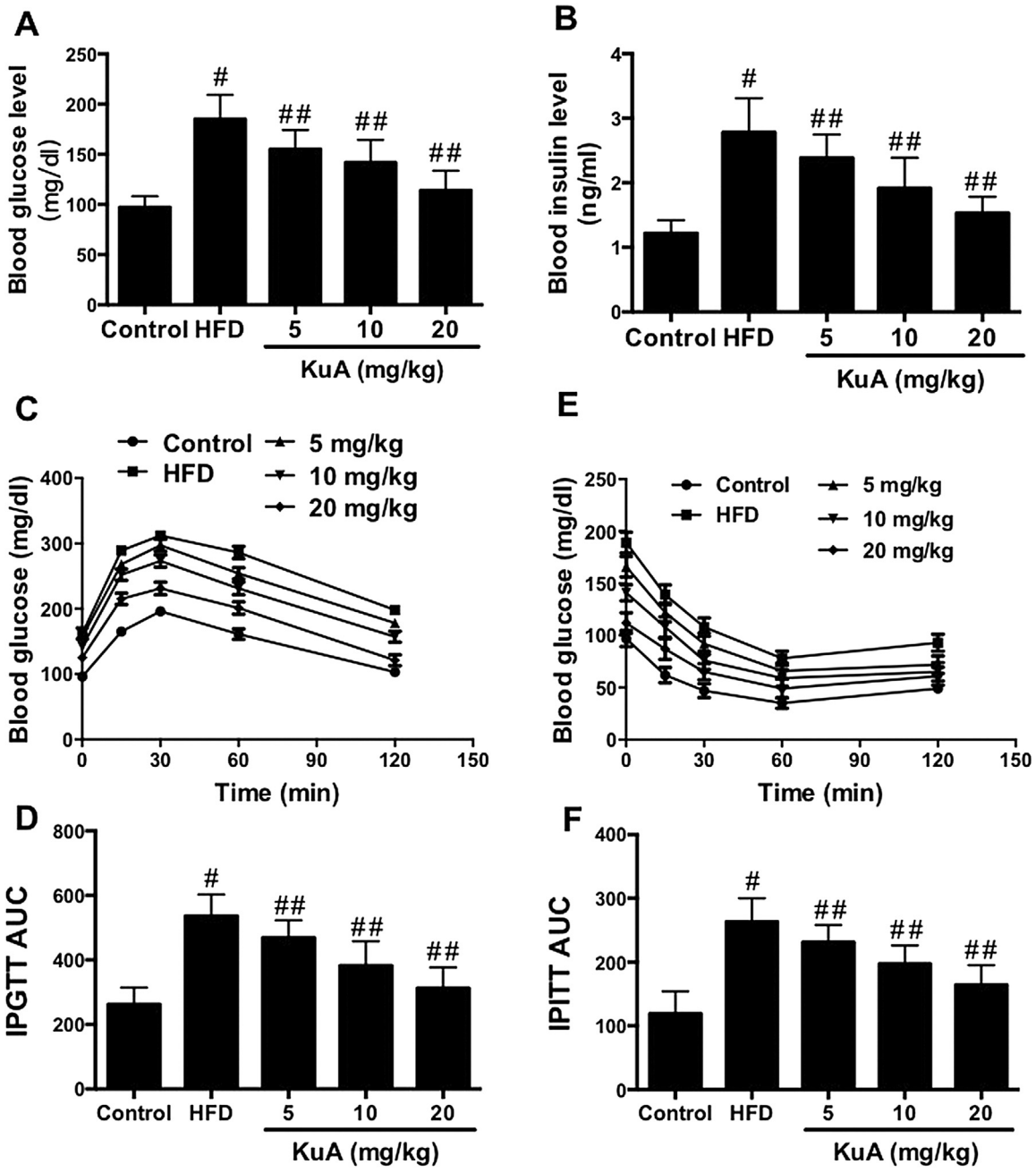

Fig. 1. Effect of KuA on insulin resistance in HFD-fed mice.
Mice were fed HFD and injected with 5–20 mg/kg KuA. Fasting blood glucose (A) and insulin (B) levels were measured. IPGTT (C and D) and IPITT (E and F) were performed to evaluate glucose and insulin tolerance. AUC was calculated based on the glucose level. #$P < 0.05$, versus control. ##$P < 0.05$, versus HFD.