Hesperidin as a Promising Anti-Diabetic Flavonoid: the Underlying Molecular Mechanism

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Diabetes mellitus is a worldwide metabolic disorder with a rapidly increasing incidence. The International Diabetes Federation (IDF) has estimated the number of patients with diabetes to be 415 million in 2015. The IDF also expected that the number of diabetic patients will increase to 642 million by 2040[1]. The currently used therapeutic options for the management of diabetes has their own limitations. Therefore, there is a greater need for safe and effective alternative anti-diabetic agents[1].

Flavonoids are a diverse group of polyphenolic compounds present in fruits, flowers and leaves of plants. This class of natural compounds is known to have potential benefits in human health[12]. Flavonoids act by modulating oxidative stress and inflammation. We carried out several studies in our laboratory to examine the antioxidant, anti-inflammatory, anti-diabetic and hepatoprotective activities of specific flavonoids[3-9].

Hesperidin is an inexpensive flavone glycoside (Figure 1) abundant in citrus fruits and isolated from the ordinary orange Citrus aurantium L. and other plants of the Family Rutaceae[10]. Numerous in vitro and in vivo studies provide evidence that hesperidin possesses beneficial effects for the prevention and treatment of diabetes. In this context, we have reported the potential anti-diabetic effects of hesperidin both in vitro[3] and in vivo[4]. Hesperidin supplementation potentially regulated the activities of glycolytic and gluconeogenic enzymes and attenuated hyperglycemia in db/db C57BL6 mice[11] and high fat diet/streptozotocin (HFD/STZ)-induced diabetic rats[4]. This compound has been reported to up-regulate peroxisome proliferator activated receptor gamma (PPARγ), hepatic glucokinase and adipocyte glucose transporter 4 (GLUT4)[7,8,12,13].

Figure 1: Chemical structure of hesperidin

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313
In HFD-STZ-induced type 2 diabetic rats, we have demonstrated the ability of hesperidin to improve blood glucose levels through attenuation of oxidative stress and production of pro-inflammatory cytokines[40]. In combination with insulin, hesperidin reversed hyperglycemia and down-regulated the generation of free radicals and pro-inflammatory cytokines in experimental diabetic neuropathy[14]. Hesperidin also showed cardioprotective effects in diabetic rats through reducing oxidative stress and apoptosis and improving the PPARγ pathway[13]. In a model of STZ-nicotinamide induced myocardial infarction diabetes, hesperidin decreased the levels of blood glucose, glycosylated hemoglobin (HbA1c), lipids and blood pressure[16]. In addition, it decreased lipid peroxidation and enhanced the antioxidant defenses in both STZ[17] and HFD/STD-induced diabetic rats[4].

Regarding its lipid-lowering tendency, hesperidin reduced circulating and hepatocyte cholesterol levels partially by suppressing hepatic 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, resulting in attenuated hypercholesterolemia and atherosclerosis[18]. It has also been reported to increase the fecal cholesterol and triglycerides excretion, and impede glucose-6-phosphate dehydrogenase (G6PDH) and fatty acid synthase[12]. Recently, we demonstrated that hesperidin can decrease intestinal glucose and cholesterol absorption, suppress hepatic glucose production and increase insulin sensitivity and peripheral glucose uptake[9].

Given its regulatory effect on glucose transporters, insulin secretion and sensitivity, oxidative stress, inflammation, peripheral glucose uptake, intestinal glucose absorption and hepatic glucose production, hesperidin can play a promising role in treating diabetes and its complications. Therefore, additional studies are required to determine the exact mechanistic pathways and the beneficial effects of hesperidin for diabetic patients.

References