

Berberine: As A Therapeutic Target for Treating Obese Diabetes

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The incidence of obesity, metabolic syndrome, and diabetes are constantly increasing around the world. Studies have shown that the overall change in the lifestyle and dietary habits as a primary contributor. Obesity develops when energy intake exceeds energy expenditure. This is the result of an imbalance between the ingestion of energy-dense foods, decreased physical activity, and the inability of the CNS to suppress appetite appropriately. Obesity is a complex disease caused by the interaction of a myriad of genetic, dietary, lifestyle, and environmental factors, which favors a chronic positive energy balance, and leads to increased body fat mass [1]. Additionally, there is a close relationship between diabetes and obesity especially type 2 diabetes, which accounts for approximately 90%. This rapid increase in the occurrence of diabetes is mostly attributed to the growing prevalence of obesity in various communities of the world, which in turn causing several metabolic diseases. Natural products are recently focused on treating the combination of these disorders because of their versatile chemical nature having a multipronged mode of action.

Berberine is an isoquinoline alkaloid isolated from various species of genus berberis, extensively used as a dietary supplement in Chinese traditional medicine. The different therapeutic activities of berberine have been investigated by researchers around the globe [2-4]. When administered orally, It exhibited anti-hyperglycemic, anti-dyslipidemia and anti-obesity activities in animal studies. The potential anti-diabetic effect has been noted in randomized controlled trials by Wei and coworker (2015) where it elicited significant benefits in improving fasting blood glucose (FBG), postprandial blood glucose (PBG), glycosylated hemoglobin, and homeostasis model assessment of insulin resistance alone as well as in combination with other oral hypoglycemic agents without serious adverse effects [5]. The metabolic activity for regulating blood glucose and lipids has been widely studied and evidenced in patients and various animal models [6]. Berberine treatment of diabetic animals increased cardiac 5'-adenosine monophosphate-activated protein kinase (AMPK) and protein kinase B (AKT) activation and reduced glycogen synthase kinase 3 β (GSK3 β) activation compared to control [7]. Its hypoglycemic effect is insulin-independent related to inhibition of mitochondrial function, stimulation of glycolysis and activation of AMPK pathway. Additionally, berberine may also act as a α -glucosidase inhibitor. Pirillo and Catapano (2015) showed that it exerts a protective role in atherosclerosis relates to its cholesterol-lowering activity. Berberine significantly increases hepatic low-density lipoprotein receptor (LDLR) expression and reduces the expression and secretion of the LDLR modulator proprotein convertase subtilisin/kexin type 9 (PCSK9). It also increases glucose utilization in adipocytes and myocytes, while decreases glucose absorption in intestinal cells, resulting in a net hypoglycemic

effect. In hypercholesterolemic animals, it significantly decreases LDL-C and total cholesterol (TC) levels and reduces aortic lesions, an effect similar to that of statins. In diabetic animals, it significantly reduces glucose levels, improves glucose tolerance, and reduces body weight gain and adipose tissue mass. In hypercholesterolemic subjects, berberine-induced a significant reduction of TC, triglycerides, and LDL-C levels and a significant increase of HDL-C levels, without major adverse effects [8].

In the newly-diagnosed type 2 diabetic patients, berberine was able to lower blood insulin level *via* enhancing insulin sensitivity. However, in patients with poor β -cell function, berberine may improve insulin secretion *via* resuscitating exhausted islets. Furthermore, berberine may have extra beneficial effects on diabetic cardiovascular complications due to its cholesterol-lowering, anti-arrhythmias and nitric oxide (NO) inducing properties. The antioxidant and aldose reductase inhibitory activities of berberine may be useful in alleviating diabetic nephropathy. Although evidence from animal and human studies consistently supports the therapeutic activities of berberine, large-scale multicenter trials are still necessary to evaluate the efficacy of berberine on diabetes and its related complications [9]. In the diabetic nephropathy rats, immunohistochemistry and Western blot examination revealed a significant increase in the MMP9 and TIMP1/2 levels, with an obvious decrease in MMP2 expression [10]. Therefore, the renoprotective effects of berberine on diabetic nephropathy might be associated with changes in the extracellular matrix through the regulation of the MMPs/TIMPs system in the rat kidney.

Hu and colleagues (2012) conducted a pilot study in obese human subjects, which showed weight loss accompanied by marked reduction in lipid levels. The same results were obtained, when studied in animals [11]. The molecular study in diabetic rats showed a significant interaction between berberine and the cytochrome P450 enzymes. Berberine exhibited the potential to modify the expression of CYPs by either suppression or enhancement of CYPs' levels. Consumption of berberine as an antihyperglycemic compound by diabetic patients might provide an extra benefit due to its potential to restore the expression of *Cyp2e1*, *Cyp3a*, and *Cyp4a* to normal levels. However, a herb-drug interaction might be of concern since any berberine-containing product would definitely cause pronounced interactions based on CYP3A4 inhibition [12]. Its supplementation reverts mitochondrial dysfunction induced by High Fat Diet (HFD) and hyperglycemia in skeletal muscle, in part due to an increase in mitochondrial biogenesis, prevention of mitochondrial dysfunction by BBR, as well as AMPK activation, were blocked in cells in which SIRT1 has been knocked-down [13].

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