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Ameliorative potential of phloridzin in type 2 diabetes-induced memory deficits in rats

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ABSTRACT

Diabetes associated oxidative stress and impaired cholinergic neurotransmission causes cognitive deficits. Although phloridzin shows antioxidant- and insulin sensitizing-activities, its ameliorative potential in diabetes-induced memory dysfunction remains unexplored. In the present study, type 2 diabetes (T2D) was induced by streptozotocin (35 mg/kg, intraperitoneal) in rats on *ad libitum* high-fat diet. Diabetic animals were treated orally with phloridzin (10 and 20 mg/kg) for four weeks. Memory functions were evaluated by passive avoidance test (PAT) and novel object recognition (NOR) test. Brains of rats were subjected to biochemical analysis of glutathione (GSH), brain-derived neurotrophic factor (BDNF), malonaldehyde (MDA) and acetylcholinesterase (AChE). Role of cholinergic system in the effects of phloridzin was evaluated by scopolamine pre-treatment in behavioral studies. While diabetic rats showed a significant decrease in step through latency in PAT, and exploration time and discrimination index in NOR test; a substantial increase in all parameters was observed following phloridzin treatment. Phloridzin reversed abnormal levels of GSH, BDNF, MDA and AChE in the brain of diabetic animals. Moreover, *in silico* molecular docking study revealed that phloridzin acts as a potent agonist at M1 receptor as compared to acetylcholine. Viewed collectively, reversal of T2D-induced memory impairment by phloridzin might be attributed to upregulation of neurotrophic factors, reduced oxidative stress and increased cholinergic signaling in the brain. Therefore, phloridzin may be a promising molecule in the management of cognitive impairment comorbid with T2D.

1. Introduction

Type 2 diabetes (T2D) is associated with complications like cardiomyopathy, retinopathy, neuropathy, nephropathy, impotence and lower limb amputation (Zheng et al., 2018). Moreover, there is 50–150% higher risk of dementia in people with T2D (Biessels et al., 2006; Cukierman et al., 2005; Strachan et al., 1997). Mechanisms proposed for cognitive impairment in T2D include insulin resistance, impaired insulin growth factor signaling, glucose toxicity, cerebrovascular injury and vascular inflammation (Goyal et al., 2016; Nakhate et al., 2018; Rask-Madsen and King, 2013; Steen et al., 2005; Xu et al., 2007). Diabetes impairs cholinergic signaling and promotes accumulation of amyloid beta, a critical initiator of Alzheimer's disease (de Oliveira, 2016; Luchsinger, 2012; Sjoholm and Nystrom, 2006). Prolonged hyperglycemia associated advanced glycation end products (AGEs) induce oxidative stress by promoting reactive oxygen species formation and impairing antioxidant defense mechanisms (Atli et al., 2004; Basta et al., 2004; Negrean et al., 2007). This creates an inflammatory milieu detrimental to hippocampal and cortical neurons, and causes cognitive deficits (Mehta and Banerjee, 2017).

Natural food components have been widely investigated as preventive and/or interventional strategy in the management of various chronic disorders (Arora et al., 2021; Kamdi et al., 2021a). It is commonly believed that apples consumption may decrease risk of T2D as they are enriched with flavonoids, phenolic acids and vitamins (Oszmiansk et al., 2008; Hyson, 2011). In apple peel extract, various polyphenols like phloridzin, rutin, chlorogenic acid, epicatechin, quercetin and caffeic acid were identified (Arabbi et al., 2004; Balasuriya et al., 2005; Tian et al., 2018). Phloridzin has been widely tested for its antidiabetic and anti-inflammatory potentials (Ehrenkranz et al., 2005).

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