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Can Tea Extracts Exert a Protective Effect Against Diabetes by Reducing Oxidative Stress and Decreasing Glucotoxicity in Pancreatic β-Cells?

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Glucose is the main physiological stimulus of pancreatic β-cells. However, chronic exposure of β-cells to elevated glucose concentrations induces glucotoxicity. In animal models of type 2 diabetes, it has been shown that several days of hyperglycemia impairs glucose-stimulated insulin secretion and increases β-cell apoptosis. In patients with type 2 diabetes, the multiple disorders caused by chronic hyperglycemia in β-cells include elevated basal insulin secretion, increased sensitivity to glucose, diminished response to insulinotropic stimuli and substantial depletion of insulin hoarding [1,2]. These defects associated with insulin resistance lead to a progressive loss of β-cell mass and function and to the onset of diabetes. It is crucial to study the mechanisms by which glucotoxicity induces β-cell failure to develop therapeutic strategies for protecting and recovering a functional β-cell mass. Several mechanisms might explain the glucotoxicity due to prolonged hyperglycemia, such as β-cell exhaustion, oxidative stress induced by free radical oxygen species, endoplasmic reticulum (ER) stress, inflammation caused by proinflammatory cytokines and chemokines, loss of neogenesis, proliferation of β-cells, and so on [3-10]. However, the precise mechanisms of glucotoxicity and its contribution to the pathology of type 2 diabetes mellitus (T2DM) are still not fully understood.

Previous reports have shown that the over-production of reactive oxygen species (ROS), primarily due to hyperglycemia, causes oxidative stress in various tissues. ROS are free radicals that are intermediate metabolites derived from oxygen metabolism in mitochondria. They play an important role in both physiology and pathology in β-cells. ROS are continuously produced by the mitochondrial electron transport system as a byproduct of the oxidative phosphorylation pathway; however, normal cells have antioxidant defenses to rapidly neutralize ROS and maintain an optimal redox potential for appropriate biological cell function [2,11]. This optimal redox balance is impaired in T2DM because of increased ROS production and insufficient endogenous anti-oxidant defenses of the β-cells. Hence, antioxidant therapy could be useful for treating T2DM. Antioxidants are reducing agents, such as thiols, ascorbic acid, or polyphenols, and are widely used in dietary supplements for the prevention of diseases, such as cancer, coronary heart disease, and various inflammatory diseases. Plants and animals have multiple types of antioxidants, such as glutathione, vitamin C, vitamin A, and vitamin E, as well as antioxidant enzymes, such as superoxide dismutase 1 and 2 (SOD1, 2), glutathione peroxidase 1 (GPX1), and catalase (CAT) [12]. Insufficient amounts of antioxidants or antioxidant enzyme activities can cause oxidative stress and damage or ultimately kill cells. Previous studies in β-cell lines, isolated rodent islets, and diabetic animal models have shown that anti-oxidants can protect β-cells against the toxic effects

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of high glucose concentrations on insulin gene expression, insulin secretion and β-cell survival. Antioxidant (pre)treatment of diabetic animal models has demonstrated several protective effects against diabetic complications, including the gradual improvement of insulin sensitivity and the enhancement of β-cell function and survival [13-16].

Tea extracts have been widely used for many centuries as a beverage in traditional medicine in Asia for treating various diseases, including urinary lithiasis, edema, eruptive fever, influenza, rheumatism, hepatitis, jaundice, and renal calculus. Tablets or capsules containing dried leaves are also available as dietary supplements. Orthosiphon stamineus (OS) is a popular medicinal plant in Southeast Asia known for its diuretic, uricosuric, antioxidant, hepatoprotective, anti-inflammatory, antidiabetic, and antihypertensive effects and for its protective action against menstrual disorders. Several therapeutic effects of OS have been ascribed to polyphenol, the most abundant compound in the leaf, which has been reported to reduce oxidative stress by inhibiting lipid hyperoxidation [17-25].

Previous studies have reported that tea extracts of medicinal plants as an alternative management of T2DM are effective in reducing oxidative stress. Akowuah et al. [26] showed that the free radical-scavenging capabilities of extracts from the dry leaves of OS were comparable to pure synthetic antioxidant butylated hydroxy anisole. Aoshima et al. [27] ascribed the antioxidant effects to polyphenols in the extracts. Syiem and Warjri [28] reported that extracts of Ixeris gracilis exerted antidiabetic and antioxidant effects, which are associated with improved activities of GPX and superoxide dismutase in the liver, kidney, and brain. Kumar et al. [29] showed that the antidiabetic activity of Melastoma malabathricum Linn. leaves is associated with increased levels of SOD, CAT, and GPX.

A portion of the beneficial effects of tea extracts might be explained by their action on the β-cells. Sriplang et al. [30] demonstrated an antidiabetic effect of aqueous extracts of OS and observed a direct stimulatory effect of the extract on insulin secretion from the perfused rat pancreas. Mechanisms other than antioxidant effects of the extracts might contribute to the improved β-cell function. Ortsater et al. [31] reported that green tea catechin exerts profound antidiabetic effects associated with reduced insulin resistance and enhanced pancreatic islet function due to reduction of ER stress. In a paper published on this issue, Lee and his colleagues [32] tested the direct effect of OS extracts on INS-1 cells and evaluated the likelihood that OS extracts could prevent glucotoxicity. They showed that hexane extracts of OS dose-dependently stimulated insulin secretion and insulin and Pdx-1 gene expression and that these effects were associated with an increased level of phosphorylation of phosphoinositide 3-kinase and Akt but not with a change in peroxide levels. Interestingly, the extracts reversed the glucotoxic effects elicited by a 3-day exposure to high glucose levels (30 mM) [32].

According to all of these studies, tea extracts seem to exert multiple beneficial effects for treating diabetes. Several effects are due to the antioxidant action of the extracts, whereas other effects are attributed to a direct action on β-cells involving a stimulation of insulin secretion and a protection against glucotoxicity. Additional studies are, however, required to determine the precise underlying mechanisms. They could help us better understand the therapeutic effects of various tea extracts in the treatment of diabetes.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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