Flavonoids as potential therapeutic agents for type 1 diabetes

Type 1 diabetes results from selective destruction of insulin-producing β-cells in the pancreatic islets and is primarily a T cell-mediated autoimmune disease directed against one or more β-cell antigens. There are numerous studies showing that proinflammatory cytokines including interleukin IL-1β, interferon IFN-γ, and tumor necrosis factor TNF-α are critically involved in the pathogenesis of type 1 diabetes [1]. The generation of reactive oxygen species (ROS) is well known to be one of the main mechanisms of such cytokine-mediated β-cell damage. In addition, nitric oxide (NO) produced through the activation of inducible NO synthase (iNOS) also appears to be participating in cytokine-mediate toxicity [2,3].

The expression and activity of the main antioxidant enzymes, such as superoxide dismutase, catalase, and glutathione peroxidase are lower in the islets β-cells than in other tissues. This low antioxidant defense capacity of β-cells and the resultant enhanced sensitivity toward oxidative stress have been considered to be an important aspect of oxygen free radical-induced damages leading to β-cells death and type 1 diabetes [2,3]. It has been demonstrated that *in vivo* overexpression of the antiapoptotic, antioxidant protein thioredoxin, catalase, and superoxide dismutase protect the β-cells from streptozotocin (STZ)-induced diabetic animals which are generally considered as type 1 diabetic animal model [2].

There is currently intensive focus on polyphenolic phytochemicals such as flavonoids. Flavonoids are a class of secondary plant phenolics found ubiquitously in fruits and vegetables as well as food products which act as pharmacological active compounds in many medicinal plants. Many of the biological action of flavonoids have been attributed to their powerful antioxidant properties, either through their reducing capacities per se or through their possible influences on intracellular redox status [4,5]. Since the beginning of 1980s, the beneficial effects of flavonoids have been studied in diabetes mellitus. Recently, it has been shown that quercetin and epicatechin, two of the most widely distributed flavonoids in plants, are capable of inhibiting the deleterious effects of STZ on the pancreatic β-cells. They inhibited STZ-induced hyperglycemia and β-cell destruction in the rat pancreas as well as blocking STZ-induced NO production and inhibition of insulin release from the isolated islets [5,6]. Interestingly, silymarin, another polyphenolic flavonoid, showed the direct cytoprotective effect on cytokine-induced pancreatic β-cell damage. Importantly, silymarin has an ability to inhibit the production of inflammatory cytokines, such as IL-1β, IFN-γ, and TNF-α, from macrophages and T-cells, which probably initiate the destruction of β-cells in development of type 1 diabetes [3]. These studies revealed that flavonoids might protect the β-cells by one or more mechanisms such as scavenging ROS, maintaining higher gluthathione level, and altering the survival/death genes ratio [3,5,6]. Since the flavonoids are relatively nontoxic, the present findings regarding the protective effects on β-cells, suggest that some of these natural components might be useful in preventing type 1 diabetes. In that regard, related studies are in progress in our lab.

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