

## **Abstract**

**Introduction:** It has been reported that prolonged use of antidepressant drugs have the diabetogenic potential and increase the risk for the development of type 2 diabetes. Among of these drugs, it has been shown that fluoxetine is cytotoxic at therapeutic concentrations on pancreatic beta-cells via induction of mitochondrial dysfunction, oxidative stress and cell death.

**Methods:** In the present study, we aimed to investigate direct effect of fluoxetine on pancreas isolated mitochondria and explore the possible mitochondrial protection potency of betanin as well-known free radical scavengers and antioxidants against its deleterious effects. Intact mitochondria were isolated with mechanical lysis and differential centrifugation from rat pancreas and treated with various concentrations of fluoxetine (0, 10, 50, 100, 500, 4000 and 8000  $\mu\text{M}$ ). Then, protective effect of betanin (100, 250 and 500  $\mu\text{M}$ ) on fluoxetine-induced mitochondrial toxicity at toxic concentration in rat pancreas isolated mitochondria was studied. The activity of succinate dehydrogenases (SDH), formation of reactive oxygen species (ROS), mitochondrial swelling, collapse of mitochondrial membrane potential (MMP), malondialdehyde (MDA) production and depletion of glutathione (GSH) were analyzed during 1 hour in rat pancreas isolated mitochondria by biochemical and flow cytometry techniques.

**Results and Discussion:** Our results showed that fluoxetine directly caused toxicity in pancreatic isolated mitochondria at concentration of 500  $\mu\text{M}$  and higher. Except MDA and GSH, fluoxetine caused significantly SDH activity reduction, MMP collapse, mitochondrial swelling and ROS formation in rat pancreas isolated mitochondria. However, our results showed that only betanin protected fluoxetine-induced mitochondrial dysfunction with the increase of SDH activity, improvement of MMP collapse and mitochondrial swelling, and reduction of ROS formation in pancreas isolated mitochondria. We can conclude that fluoxetine is directly toxic on pancreas isolated mitochondria, which may be related to its diabetogenic potential in humans. Moreover, our finding suggested that use of betanin as a natural antioxidant and food colorant may be beneficial for prevention of diabetogenic effect of fluoxetine.

**Key Words:** Antioxidants; Betanin; Diabetes; Diabetogenic Effects; Diabetes Prevention