**Abstract**

**Introduction:** It has been reported that prolong 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 preset study, we aimed to investigate direct effect of fluoxetine on pancreas isolated mitochondria and explore the possible mitochondrial protection potency of thymoquinone as well-known free radical scavengers and antioxidants against its deleterious effects. Intact mitochondria were isolated with mechanical lysis and differential centrifugation form rat pancreas and treated with various concentrations of fluoxetine (0, 10, 50, 100, 500, 4000 and 8000 μM). Then, protective effect of thymoquinone (10, 50 and 100 μM) 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 μM 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 presence of thymoquinone had no impact on mitochondrial toxicity induced by fluoxetine. 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 thymoquinone, in the form of the parent molecule, not metabolized by cellular and tissue reductases did not show antioxidant and ROS scavenger activities in rat pancreas isolated mitochondria in presence of fluoxetine.

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