

## EFFECT OF EXPERIMENTAL DIABETES ON MEMBRANE FUNCTIONS AND ITS REVERSAL BY ANTIDIABETIC COMPOUNDS

**Scholar:** Mohammed Rizwan Siddiqui

**SUPERVISOR:** Dr. M. EJAZ HUSSAIN

Department of Biosciences, J.M.I., New Delhi.

**CO-SUPERVISOR:** PROF. NAJMA Z BAQUER

School of Life Sciences, J.N.U., New Delhi.

**Introduction:** Diabetes mellitus is characterized by chronic hyperglycemia and disturbance of carbohydrate, protein and fat metabolism. The condition results when there is an inadequate production or defective action of the hormone insulin. According to the WHO, report on diabetes, in 2004, more than 150 million people worldwide suffer from one or the other form of diabetes. Diabetes mellitus is the most common cause of adult renal failure and blindness worldwide. Insulin, since its discovery has been used as a life saving therapy for diabetes. Exogenous insulin, however, fails to produce a well-controlled status and does not effectively prevent the long-term complications associated with diabetes. In Type 2 diabetes, insulin is relatively ineffective because of insulin resistance of the responding tissues. Various oral hypoglycemic drugs like sulphonylureas, thiazolidinediones and biguanides are also being used for the treatment of diabetes. However, these drugs often cause hypoglycemia and other toxic conditions. Thus there is a need to find new drugs that are potent, safe and cost effective. In this study, the insulin mimetic and the antidiabetogenic properties of various trace metals (vanadium) and natural agents (*Trigonella*) have been studied.

**Methodology:** The present work investigates the prospect of using low doses of vanadate in combination with *Trigonella foenum graecum* seed powder and evaluates their antidiabetic effect in alloxan-diabetic rats. Alloxan induced diabetic rats were treated with insulin (2units/rat/day), vanadate (0.6mg/ml), and 5% *Trigonella* alone and with a combined dose of vanadate (0.2mg/ml) and *Trigonella* for 21 days and the animals were then used to study the metabolic changes in various tissues (liver, kidney, heart and brain). Different parameters studied were: General physiological parameters,  $\text{Na}^+/\text{K}^+$  ATPase and  $\text{Ca}^{+2}$  ATPase and Expression of  $\text{Na}^+/\text{K}^+$  ATPase alpha-1 isoform protein, Monoamine (MAO) oxidase enzyme, Membrane lipid peroxidation and membrane lipid fluidity, Expression and distribution of Glucose transporter (GLUT4), DNA degradation/fragmentation.

**Results:** The decreased body weight and increased blood glucose level caused due to

diabetes induction was restored by insulin, *Trigonella* and *Trigonella* and vanadate in combination, administered to diabetic rats. Significant changes were observed in the activities of Na<sup>+</sup>/K<sup>+</sup> ATPase, Ca<sup>2+</sup> ATPase, MAO, Lipid peroxidation and Membrane fluidity in diabetic tissues. These were also restored to normal levels by insulin, *Trigonella* and combined dose of vanadate and *Trigonella*. There was a marked decrease in the GLUT4 protein levels in the membrane fractions of the heart and skeletal muscle of diabetic animals. Immunohistochemical data of the diabetic skeletal muscle also showed the decreased distribution of GLUT4 protein. Oxidative DNA degradation was increased in the diabetic animals as compared to the age matched controls. Treatment of diabetic rats with antidiabetic compounds for 21 days restored the GLUT4 levels and DNA degradation to the control levels.

**Conclusion: Antidiabetic potential of vanadate and *Trigonella*:**

The data from the present results conclude that the lower doses of vanadate could be effectively used with *Trigonella* seed powder to counter the diabetes-induced alterations related to membrane functions in alloxan-diabetic rats. Low doses of vanadate when given to control rats did not result in weight loss of animals; the blood glucose levels were also not affected. However, when diabetic rats were treated with low doses of vanadate for three weeks, it could not lower hyperglycemia. Thus vanadate shows less toxicity at lower doses but fails to elicit any antidiabetic effects. In this research work, the toxicity of vanadate was reduced by using lower doses and combining it with *Trigonella* seed powder. The lower doses of vanadate in combination with *Trigonella* effectively controls physiological parameters, plasma glucose levels and normalizes alterations in the key membrane functions of the cell and can indeed be considered as an alternative to be explored further for clinical trials as a means of amelioration of diabetes in human subjects.