6. SUMMARY

Effective blood glucose control is the key in preventing or reversing diabetic complications and improving quality of life in patients with diabetes. The herbal treatment for diabetes focuses on goals and strategies for the treatment and prevention of diabetes and on achieving metabolic outcomes related to hyperglycemia without any or less side effects. Alternative therapies with antidiabetic activity have been researched extensively all over the world. Due to the adverse effects of currently available antidiabetic agents, global epidemic have encouraged a strong effort over the world to discover drugs that can manage diabetes more effectively.

Gymnema species are traditionally used to treat disorders such as diabetes, high cholesterol, wounds, inflammation and gastrointestinal ailments. *G. montanum* H. belonging to the family Asclepiadaceae is an endemic plant species of India found mainly in the Shola forests of Western Ghats, The Nilgiris. Since some members of the Gymnema species (*G. sylvestre*, *G. inodorum* and *G. yunnanense*) have been reported to posses antidiabetic properties, it is expected that *G. montanum* also contain antidiabetic properties which has been explored in this study.

The effect of ethanol extract of *G. montanum* leaves on blood glucose, plasma insulin, oral glucose tolerance test, carbohydrate and lipid metabolism, lipid peroxidation and antioxidant status was studied in the alloxan-induced diabetic rats. The modulatory proteins which could be the effective target in antidiabetic property of this plant were studied using proteomics approach. Its protective effect on oxidative DNA damage was also studied using human peripheral blood lymphocytes and HL-60 cell line. Further the possible active principle compound from *G. montanum* was isolated and characterized. Its effect on oxidative stress induced apoptosis in insulin secreting rat insulinoma cell line (RINm5F) was also studied.

Treatment of alloxan-induced diabetic rats with aqueous and ethanol extracts of *G. montanum* showed significant antihyperglycemic activity. The maximum reduction in glucose levels was observed in rats receiving 200 mg/kg of GLEt. Although higher dose (400 mg/kg GLEt) also showed blood glucose lowering activity, the magnitude of reduction was less compared to that of 200 mg/kg dose. On the other hand, in GLAt-treated animals the antihyperglycemic effect was observed much later compared to those treated with GLEt.
Histological observation of liver, kidney and pancreas of diabetic rats indicated fatty infiltration and shrinkage of islets in pancreas, sinusoidal congestion and fatty degeneration in liver and fatty infiltration and parenchymal inflammation in kidney. GLEt treatment for 3 weeks markedly reduced these pathological changes.

The administration of GLEt to alloxan-induced diabetic rats significantly decreased the blood glucose level with significant increase in plasma insulin activity. Administration of GLEt to diabetic rats significantly increased Hb content and significantly decreased the HbA1c levels. GLEt administration effectively prevented the increase in blood glucose without causing a hypoglycemic state which was studied using oral glucose tolerance test. Administration of GLEt to diabetic rats reversed the diabetic related changes in the activities of hepatic carbohydrate metabolic enzymes hexokinase, glucose-6-phosphate dehydrogenase, glucose-6-phosphatase and fructose-1,6-bisphosphatase and its glycogen content.

Administration of GLEt significantly decreased the diabetic associated lipid peroxidation which was measured by the markers such as TBARS and hydroperoxides, accompanied with significant increase in the activities of enzymic antioxidants SOD, CAT, GPx and GST as well as non-enzymic antioxidant GSH. The levels of total cholesterol, HDL-C, LDL-C and VLDL-C, triglycerides, free fatty acids and phospholipids were positively modulated by the administration of GLEt. The increased activity of HMG-CoA reductase in alloxan-induced diabetes was significantly reduced by GLEt.

Proteomic analysis of diabetic rat serum samples indicated that 12 proteins were significantly modulated in comparison to normal rat serum. Among them, two proteins were found to be up-regulated and other 10 proteins were found to be down-regulated, although the order of magnitude of the changes differed widely. Among them, seven proteins were modulated either increased or decreased to normal level by GLEt treatment. GLEt confers significant protection in both the cell types (human peripheral blood lymphocytes and HL-60) against oxidative DNA damage caused by H$_2$O$_2$ whereas the magnitude of the protective effect was found to be less in MMS induced DNA damage. The global percent repair efficiency showed that GLEt treatment provided effective protection against H$_2$O$_2$-induced
DNA damage but not as effective against MMS. Its repair capacity against $\text{H}_2\text{O}_2$ induced DNA damage was comparable to that of vit-C.

Further one active principle compound having basic skeleton resembling stigmasterol was isolated from the plant extract and was found to be effective in preventing oxidative stress induced apoptosis in RINm5F cells.

The results of the present study demonstrated the antidiabetic effect of *G. montanum* on the carbohydrate metabolism, lipid metabolism and lipid peroxidation. It is also found to contain antigenotoxic property primary through its antioxidant effect.

Further the isolated phytosterol from this extract exhibited antiapoptotic effect. The proteomic profile of the control and experimental rat serum samples showed the modulation in the protein pattern which involved in the hyperglycemic regulation. These findings strengthen the observation that naturally occurring compounds of plant origin are effective against diabetes and its complications. In particular, *G. montanum* and the isolated sterol represent a potential source for discovery of new orally active component(s) for future therapy and a promising approach for intervention and prevention of progression of diabetes mellitus.