Chapter 6
Conclusion

Strategies to mitigate oxidative stress have currently become a significant pharmacotherapy in the treatment of diabetic complications. The importance of maintaining the redox balance and reducing the blood glucose levels plays important role in combating diabetic micro and macrovascular complications [340]. The results of this study indicate that antioxidant Resveratrol shows positive effects on oxidative stress pathway genes, insulin signalling pathway genes, MAPK signalling and PPAR signalling under in vitro stress conditions. Resveratrol is the most potent followed by Baicalein, Curcumin, and Carvacrol amongst the four studied dietary antioxidants. Resveratrol along with insulin performed the best to scavenge ROS generated during stress. The analysis of SOD, CAT, GPx, and GST gene with different treatment combinations along with different antioxidants indicates that the highest expression was found in cells treated with insulin and antioxidant treatment combination, from the experimentations performed during the course of this thesis we can draw a conclusion that the antioxidants along with insulin work best to scavenge ROS generated
during stress. Although previous studies have confirmed the potential of Insulin to combat diabetes solely, we observed that insulin in combination with the dietary and natural antioxidant was mostly more effective. Further experiments have been performed in *in vivo* models to provide more affirmative results regarding the exact potency of the best performing antioxidants (under *in vitro* conditions). The findings of the *in vivo* study showed that oral administration of Resveratrol and Baicalein to STZ-NA induced diabetic rats significantly lowers the blood glucose level and has a similar effect as the oral hypoglycemic drug Glibenclamide in reducing the alterations in various biochemical parameters such as TC, TG, HDL, LDL, AST, ALT, plasma insulin, urea and uric acid under diabetic stress conditions. Resveratrol and Baicalein showed potential oxidative stress amelioration in STZ-NA induced diabetic rats which were ascertained by improved glycemic levels and reduced lipid peroxidation levels along with improved antioxidant enzymatic activities. Moreover, both the antioxidant Resveratrol and Baicalein increased the mRNA levels of *SOD, CAT, GPx* and *GST* in the liver tissues, as well as enhanced the mRNA levels of *PPARγ* and *FALDH* in adipose tissue of STZ-NA induced diabetic rats. Antioxidant therapy is a potential future therapeutic strategy by increasing the level of antioxidant in patients with DM-induced oxidative damage that may hopefully counter the effects of oxidative stress and inflammation, thereby reducing the severity of diabetic complications. The intervention for oxidative stress reduction is necessary for the overall therapy of diabetes which highlights the importance of antioxidants such as Resveratrol, Carvacrol, Curcumin and Baicalein in the treatment of diabetes. In the comparative analysis, Resveratrol was found to be more potent antioxidant, antihypereglycemic and antidyslipidemic efficacies as compared to the other three tested antioxidant molecules, suggesting that Resveratrol holds enormous potential in controlling oxidative stress mediated hyperglycemia in *in vitro* and *in vivo* models. Therefore, the present study may contribute to future studies to develop pharmacological targets for
novel therapies to prevent, reverse, or delay the onset of diabetes and its related complications.

Another aspect of this thesis was to explore the possible SNP association study of T2D variants with anthropometric parameters. The associations of T2D variants with BMI, family history, and LDL levels, were replicated to unreveal the common mechanism underlying T2D and measures of obesity. The results obtained above indicate that for the selected genes, more than 50% of the T2D population is carrying the mutations. Our study further highlights the strong association of *FTO* (rs9939609) and *SLC30A8* (rs166634) observed with high BMI levels with T2D pre-disposition. Hence, both these biomarkers could serve as a potential tool to tailor therapy for T2D prevention and management in the North East Indian population. From the MDR analysis, it can be concluded that *KCNJ11* with *SLC30A8* polymorphisms together and *KCNJ11* and *FTO* together could be used to independently predict T2D in our population. The gene-gene interaction data obtained can be used for developing a panel of genes required to be used as T2D risk markers. This present study has some limitations to be addressed like all SNPs involved in the study have been authenticated to be type 2 diabetes susceptible SNPs previously; thus any novel loci could not be established by our work. However, our study is the first of its kind to investigate the susceptibility genes to T2D in the North Eastern region of India.