9. SUMMARY AND CONCLUSIONS

In conclusion, results of this study showed that Nrf2 is an attractive druggable target for diabetes, and targeted activation of its expression helps to prevent diabetes. To date, several phytochemicals, as well as synthetic small molecule activators of Nrf2 have been identified. However, only a few could reach clinical trial stages, albeit with minimal success. Therefore the search for more potent and safe Nrf2 activators continued. The data presented in this study showed that naringenin is a potent activator of Nrf2, hence, could be considered for the further development of potent anti-diabetic agents.

Naringenin exhibited radical scavenging properties in vitro as evidenced by its ability to neutralize (a) hydroxyl radicals; (b) superoxide; (c) hydrogen peroxide; (d) nitric oxide radical; (e) DPPH and (f) lipid peroxidation in a dose-dependent manner. In MIN6 cells naringenin increased the expression of Nrf2 and promoted its’ translocation into the nucleus. The translocated Nrf2 activated target genes NQO1 and GST thereby mitigated the STZ-induced pancreatic β-cell apoptosis in MIN6 cells by decreasing caspase-3 and reducing ROS levels.

In animals, administration of naringenin reduced the complications of MLDSTZ-induced diabetes by inhibiting key enzymes in gluconeogenesis as well as by activating the pathway leading to the (a) synthesis of glycogen and (b) degradation of glucose ie., glycolysis. In essence, naringenin exerted anti-hyperglycemic action by normalizing the disturbance of carbohydrate metabolism via enhancing glucose utilization through increased glycolysis and glycogen synthesis and by decreasing hepatic glucose production through gluconeogenesis and glycogenolysis. In addition, oral administration of naringenin to mice with experimental diabetes mellitus significantly normalized the altered levels of serum insulin. Furthermore, treatment with naringenin normalized the altered levels of serum hepatic markers enzymes including SGOT, SGPT, ALP, and GGT. Furthermore, naringenin exerted its anti-hyperlipidemic action by restoring the levels of enzymatic (SOD, CAT, GPX, and GST) and non-enzymatic (GSH) antioxidants to near normal states and by decreasing the intensity of lipid peroxidation. Histopathological studies also suggested that naringenin confers protection against oxidative damage in pancreas, liver, and kidney tissues of STZ treated mice. In addition, immunohistochemical analysis of pancreas collected from diabetic mice treated with naringenin exhibited insulin-positive cells with improved β-cell mass.

In conclusion, the in vitro and in vivo results of the present study highlight the potential of naringenin to activate Nrf2 and protect the pancreatic β-cells against oxidative damage. Above findings provide key evidence to demonstrate that naringenin is a good anti-diabetic agent. However, further studies testing the safety and efficacy of naringenin in higher animals are required to bring this natural product to the clinic. Additionally, strategies improving the delivery of naringenin are also warranted to reduce the dose as well as to enhance the potency.