Summary and Conclusion

The need for alternative strategies for the prevention and treatment of metabolic disorders is growing rapidly, as Type 2 diabetes is reaching epidemic status in our society. This need forms the basis for the creation of the whole study, as it was necessary to start looking towards medicinal plants as potential antidiabetic treatment. Traditional knowledge and historic literatures on ethnomedicine provide another aspect of clues for discovering potential therapeutic agents say for the plant *Sapindus trifoliatus* is a well known drupe, and has been used as a natural surfactant for thousands of years in Asia and North America. Soapnuts have been long in folk remedies as a mucolytic agent, emetic, contraceptive and for treatment of excessive salivation, epilepsy, and to treat chlorosis However, the biological activities of this plant remain poorly understood. Thus, this study is designed to investigate the scientific basis for their traditional usage in the treatment of Diabetes mellitus and also comprehensively explain about the mechanism of action of particular active component i.e Hederagenin.

Hederagenin are basically saponins, which is a type of secondary metabolic product abundant in their fruits, the *in vivo* studies explored the possible antidiabetic effect of saponins in high-fat diet and low-dose streptozotocin (STZ) induced T2DM mice. The *in vitro* studies clearly indicated that Hederagenin inhibits DPP IV and increases the production of insulin. Inhibition of DPP IV is an attractive new approach to the treatment of Type 2 diabetes. Because DPP IV inhibitors stimulate insulin secretion in a glucose dependent fashion, the potential for hypoglycemic side effects is minimal.

Patients with Type 2 diabetes require a stepwise management approach. Initial management involves lifestyle modifications and treatment with antihyperglycemic agents. If targets are not achieved, then a combination therapy of oral agents and insulin is used. However, oral anti hyperglycemic drugs available now have not been shown to alter the progressive β cell failure, and the current combination therapy for Type 2 diabetes may be associated with an increased risk of adverse effects, such as, hypoglycemia and gain in bodyweight.
A recent pan-European cross-sectional diabetes study, PANORAMA, reported that 37.6% of patients had not met a target of HbA1c <7.0%. Furthermore, approximately 45% of the patients in the study were obese (BMI >30 kg/m²), 55% had elevated total cholesterol, and more than 80% were hypertensive. By comparison, in the United States, only 57% of patients with Type 2 diabetes achieve an HbA1c level <7.0%. Control across multiple parameters is difficult to achieve with <15% of patients meeting their targets for HbA1c, blood pressure, and low-density lipoprotein (LDL) cholesterol. Despite the challenges, achieving sustained improvements across multiple parameters (HbA1c, weight, and blood pressure) is critical for optimising outcomes for patients with Type 2 diabetes.

Type 2 Diabetes mellitus is always associated with imbalance of human metabolism and some changes in work patterns from heavy labour to sedentary, the increase in computerization and mechanization, and improved transport are just a few of the changes that have had an impact on human metabolism. The lack of weight gain, and potential for weight loss, with DPP IV inhibitor treatment provides another potential benefit to diabetics, the vast majority of whom are obese. Finally, recent data suggesting restorative effects on pancreatic islets provide hope that DPP IV inhibitors will slow or perhaps reverse the course of disease. The promise of this treatment remains to be realized as potent and selective inhibitors progress through clinical studies.

Tumor necrosis factor-α (TNF-α) is a potent cytokine that was originally identified as a factor with a wide range of pro-inflammatory activities. However, later on, an important role of TNF-α in the pathogenesis of insulin resistance was also indicated, as many human studies showed a relationship between serum TNF-α levels and insulin resistance, and mice lacking the TNF-α gene were less insulin-resistant than wild-type mice. Therefore, TNF-α seems to impair insulin action, and, thus lead to the development of Type 2 diabetes. The association of the TNF-α gene polymorphisms with DM and its related conditions, such as insulin resistance and obesity, has been extensively examined.
In comorbid conditions, the antioxidant defence system representing a complex
network with interactions, synergy and specific tasks of antioxidant is depleted in
Type 2 diabetic patients resulting in oxidative stress and resultant tissue damage
which stands as the hallmark of chronic diseases and cell death. It was recently
discussed some of the paradigms of oxidative stress in diabetes, occurs at an early
stage in diabetes, preceding the appearance of complications, or whether it is merely
a common consequence of the tissue damage reflecting the presence of complication, is a matter of scientific debate. But, it is true that oxidative stress
plays an important role in diabetic complications. Argument was made that
treatment of diabetes with antioxidant therapy is like applying water to a burning
house and is certainly helpful in limiting the conflagration. Obviously, finding out
the real cause and understanding becomes the secondary consideration to be
explained and addressed later. Nonetheless, Hederagenin also proved to be an
antioxidants, and helps in retrieving the normal healthy anti-oxidant mechanism.

The medical therapy of NAFLD and non-alcoholic steatohepatitis is an arena of
significant research. Currently, there is no approved therapy for NAFLD. There are
many proposed agents being evaluated, each targeting a different step in the
pathogenesis of development of hepatic steatosis or its progression to steatohepatitis
The modulation of cytokines associated with hepatic steatosis and its associated
inflammation and fibrosis has become a recent focus of research. Circulating levels
of TNF-α have been demonstrated to be elevated in patients with non-alcoholic
steatohepatitis compared to control patients Therefore, therapeutic options targeting
TNF-α appear as rational treatments for non alcoholic steato hepatitis. With this
basic idea, a study was conducted in C57BL6 mice by feeding high fat diet, Hederagenin thoroughly reduced the liver damage and the progression of disease.

Genetic toxicology assays was also carried on to confirm that the potential herbal
drug or lead molecule is not mutagenic or carcinogenic. Hederagenin, proved to be
non-mutagenic at specific concentrations culture measured by the chromosomal
aberration assay using human lymphocyte in the absence or presence of S9 mix.
Hence, it is concluded that Hederagenin does not have the capacity to induce
chromosomal damage in CHO cells at the mentioned dose levels and on this basis alone proved that Hederagenin does not cause any a genetic hazard to mankind.

In conclusion, Hederagenin proved the improving effect of glucose tolerance in diabetic conditions and also have been found to improve dyslipidemia in animals by addressing multiple targets associated with combination of preventing the β-cell destruction, histological architecture of the pancreatic islets, improving glucose disposal by inhibiting DPP IV, enhancing endogenous enzymatic antioxidant in liver and the pathology of DM. Multi-targeted approaches, such as anti-oxidant, hyperlipidemia and non alcoholic fatty liver disease, multiply the number of pharmaco- logically relevant targets by introducing a set of indirect, network dependent cascade with no identified side effects and toxicity. This exemplifies an approach with potential therapeutic value and balanced outcome.

**De novo (New Beginning)**

These outcomes of the work deserve further studies to be done to substantiate these observation and to increase their clinical relevance. Further work that can be done based on the outcome of this thesis has been outlined below.

**Combinational therapy**

Long-term studies can be done by using different subgroups of animals, along with possible combination of DPP IV inhibitors in market, such as newly diagnosed patients versus Animals with an advanced diseases/genetically modified conditions can also be used in the study.

_In future, formidable challenges are to yet to be met before diabetes can be studied in detail aided by the model truly reflecting its complexity. Nevertheless, the experimental efforts already undertaken have advanced our understanding of the disease._