### Contents

Title page
Declaration
Certificate
Acknowledgement
Contents
List of tables
List of figures
Abbreviations

1. Introduction .............................................. ................................. 1
2. Literature Review ........................................................... ..................... 4
   2.1 Diabetes definition and classification ................................. 4
      2.1.1 Historical Background .................................................. 4
      2.1.2 Classification ................................................................ 5
   2.2 Type 1 Diabetes Mellitus ....................................................... 7
      2.2.1 Pathophysiology of Type 1 diabetes mellitus .............. 8
      2.2.2 Animal models of type 1 diabetes mellitus ................. 23
   2.3 Type 2 Diabetes Mellitus .......................................................... 32
      2.3.1 Risk Factors ......................................................................... 32
      2.3.2 Pathophysiology of Type 2 Diabetes Mellitus ............. 34
      2.3.3 Animal models of type 2 diabetes .................................. 62
   2.4 *Punica granatum* ................................................................. 71
   2.5 *Nelumbo nucifera* ................................................................. 82
3. Experimental ........................................................................................ 92
4. Results ........................................................................................................ 106
5. Discussion .............................................................................................. 145
6. Conclusion ............................................................................................. 158

References
List of tables

Table 1  ADA classification of diabetes mellitus
Table 2  Major β-cell autoantigens associated with immune related type 1A diabetes mellitus
Table 3  Examples of interventions preventing IDDM in animal models
Table 4  Risk for diabetes in relatives of patients
Table 5  Correlation of cytokines expressed in islets with β-cell destructive or benign insulitis
Table 6  Effects of cytokine additions to islets in vitro and to NOD mice and BB rats by systemic administration
Table 7  Effects of cytokine deletions in NOD mice and BB rats
Table 8  Comparative features of type 1 DM in different animal models and human
Table 9  Different transgenic models in NOD mouse
Table 10  Different genes knock out models in NOD mouse
Table 11  Different facilitative glucose transporters in mammals
Table 12  Concentration of GLUT 4 in animal models with altered insulin levels and sensitivity
Table 13  Changes in concentration of GLUT 4 in different conditions in humans
Table 14  Phytochemical constituents of flowers of P. granatum and N. nucifera
Table 15  TLC solvent systems for methanolic extracts of P. granatum and N. nucifera
Table 16  HPTLC peak table of methanolic extract of P. granatum
Table 17  HPTLC peak table of methanolic extract of N. nucifera
Table 18  In-vitro free radical scavenging activity with DPPH
Table 19  Effect of drugs on blood glucose of normal fasted rats
Table 20  Effect plant extracts on the oral glucose tolerance of normal fasted rats
Table 21  Effect of extracts on the blood glucose levels of streptozotocin-induced diabetic rats
Table 22  Effect of drugs on blood glucose of streptozotocin-induced diabetic rats
Table 23  Effect of drugs on serum lipid profile of streptozotocin-induced diabetic rats
Table 24  Effect of drugs on serum insulin levels of streptozotocin-induced diabetic rats
Table 25 Effect of drugs on activities of hepatic enzymes of streptozotocin-induced diabetic rats
Table 26 Effect of drugs on body and liver weight of streptozotocin-induced diabetic rats
Table 27 Effect of drugs on blood glucose of streptozotocin-nicotinamide induced diabetic rats
Table 28 Effect of drugs on insulin sensitivity (K_{ITT}) of streptozotocin and nicotinamide-induced diabetic rats
Table 29 Effect of drugs on serum lipid profile of streptozotocin-nicotinamide induced diabetic rats
Table 30 Effect of drugs on serum insulin levels of streptozotocin-nicotinamide induced diabetic rats
Table 31 Effect of drugs on activities of hepatic enzymes of streptozotocin-nicotinamide induced diabetic rats
Table 32 Effect of drugs on body and liver weight of streptozotocin-nicotinamide induced diabetic rats
Table 33 Effect of drugs on blood glucose of high fat fed rats
Table 34 Effect of drugs on insulin sensitivity (K_{ITT}) of high fat fed rats
Table 35 Effect of drugs on serum lipid profile of high fat fed rats
Table 36 Effect of drugs on serum insulin levels of high fat fed rats
Table 37 Effect of drugs on activities of hepatic enzymes of high fat fed rats
Table 38 Effect of drugs on body and liver weight of high fat fed rats
List of Figures

Figure 1 Insulin Stimulated Glucose Transport
Figure 2 HPTLC chromatogram of methanolic extract of *P. granatum*
Figure 3 HPTLC plates of methanolic extracts of *P. granatum*
Figure 4 HPTLC chromatogram of methanolic extract of *N. nucifera*
Figure 5 HPTLC plates of methanolic extracts of *N. nucifera*
Figure 6 *In-vitro* free radical scavenging activity of extracts with DPPH
Figure 7 Effect of 21 days treatment of extracts of PG and NN on blood glucose of streptozotocin-induced diabetic rats
Figure 8 Effect of 21 days treatment of extracts of PG and NN on serum cholesterol levels of streptozotocin-induced diabetic rats
Figure 9 Effect of 21 days treatment of extracts of PG and NN on serum HDL and LDL levels of streptozotocin-induced diabetic rats
Figure 10 Calibration plot for insulin ELISA
Figure 11 Effect of 21 days treatment of extracts of PG and NN on serum insulin levels of streptozotocin-induced diabetic rats
Figure 12 Effect of 21 days treatment of extracts of PG and NN on activities of hepatic enzymes of streptozotocin-induced diabetic rats
Figure 13 Effect of 21 days treatment of extracts of PG and NN on body weight of streptozotocin-induced diabetic rats
Figure 14 Effect of 21 days treatment of extracts of PG and NN on blood glucose of streptozotocin-nicotinamide induced diabetic rats
Figure 15 Effect of 21 days treatment of extracts of PG and NN on insulin sensitivity (K_{ITT}) of streptozotocin and nicotinamide-induced diabetic rats
Figure 16 Effect of 21 days treatment of extracts of PG and NN on serum cholesterol levels of streptozotocin-nicotinamide induced diabetic rats
Figure 17 Effect of 21 days treatment of extracts of PG and NN on serum LDL and HDL levels of streptozotocin-nicotinamide induced diabetic rats
Figure 18 Effect of 21 days treatment of extracts of PG and NN on serum insulin levels of streptozotocin-nicotinamide induced diabetic rats
Figure 19 Effect of 21 days treatment of extracts of PG and NN on activities of hepatic enzymes of streptozotocin-nicotinamide induced diabetic rats

Figure 20 Effect of 21 days treatment of extracts of PG and NN on body weight of streptozotocin-nicotinamide induced diabetic rats

Figure 21 Effect of 21 days treatment of extracts of PG and NN on blood glucose of high fat fed rats

Figure 22 Effect of 21 days treatment of extracts of PG and NN on insulin sensitivity (KITT) of high fat fed rats

Figure 23 Effect of 21 days treatment of extracts of PG and NN on serum cholesterol levels of high fat fed rats

Figure 24 Effect of 21 days treatment of extracts of PG and NN on serum LDL and HDL levels of high fat fed rats

Figure 25 Effect of 21 days treatment of extracts of PG and NN on serum insulin levels of high fat fed rats

Figure 26 Effect of 21 days treatment of extracts of PG and NN on activities of hepatic enzymes of high fat fed rats

Figure 27 Effect of 21 days treatment of extracts of PG and NN on body and liver weight of high fat fed rats
List of Abbreviations

BB rats - Biobreeding rats
BBDP/Wor - Diabetes-Prone BioBreeding rats, colony from Worcester
BBDR/Wor - Diabetes-Resistant BioBreeding rats, colony from Worcester

cAMP - Cyclic Adenosine Monophosphate
DM - Diabetes Mellitus
DZ - Dizygotic
ELISA - Enzyme Linked Immunosorbant Assay
ES - Embryonic Stem cells
FFA - Free Fatty Acid
FPIR - First-Phase Insulin Release
GAD - Glutamic Acid Decarboxylase
GH - Growth Hormone
GIP - Glucose-Dependent Insulinotropic Polypeptide
GLP-1 - Glucagon Like Peptide-1
GLUT - Glucose Transporter
HFF - High Fat Fed
HLA - Human Leukocyte Antigen
HSL - Hormone Sensitive Lipase
IAA - insulin autoantibodies
ICA - Islet Cell Antibody
ICARUS - Islet Cell Antibody Registry of Users
IDDM - Insulin Dependant Diabetes Mellitus
IFN - Interferon
IGF - Insulin Like Growth Factor
IGT - Impaired Glucose Tolerance
IL - Interleukin
IRS - Insulin Receptor Substrate
IVGTT - Intravenous Glucose Tolerance Test
K_ATP - ATP sensitive K⁺ channel
LAR - Leukocyte Related Antigen
MAPK - Microtubule Associated protein Kinase
MHC - Major Histocompatibility Complex
MZ - Monozygotic
NAD - Nicotinamide Adenine Dinucleotide
NEFA - Non-esterified Fatty Acid
NIDDM - Non-Insulin Dependant Diabetes Mellitus
NOD - Non Obese Diabetic
PARP - Poly (ADP-Ribose) Polymerase
PCR - Polymerase Chain Reaction
PGDF - Platelet-Derived Growth Factor
PI3K - Phosphatidylinositol 3-Kinase
PKA - Protein Kinase A
PTP - Protein Tyrosine Phosphatase
Ser - Serine
STZ - Streptozotocin
TGF - Transforming Growth Factor
TNF - Tumour Necrosis Factor
Tyr - Tyrosine
ZDF rats - Zucker Diabetic Fatty rats