6. SUMMARY AND CONCLUSIONS

Diabetes mellitus (DM)) or simply diabetes is a group of metabolic disorder of multiple etiology characterized by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both. The effects of diabetes mellitus include long-term damage, dysfunction and failure of various organs. The more prevalent form of diabetes is type 2 diabetes which accounts for more than 90% of cases. The pathogenesis of type 2 diabetes is complex and involving progressive development of insulin resistance and a relative deficiency in insulin secretion. The burden of this disorder is enormous, owing to its rapidly increasing global prevalence, the devastating damage it can do to many organs of the body, and the direct and indirect costs. The estimated worldwide prevalence of diabetes among adults was 285 million (6.4%) in 2010, and this value is predicted to rise to around 439 million (7.7%) by 2030. The pandemic of type 2 diabetes, along with its high human and economic costs, is showing no signs of abatement and, therefore, new approaches are urgently needed to prevent, slow the progression, and limit the consequences of this disease.

The treatments of diabetes include diet, exercise, use of oral hypoglycemic agents and insulin is the primary forms of treatment for diabetes. Currently available synthetic anti-diabetic agents besides being expensive produce serious side effects. Apart from currently available therapeutic options, traditional medicines or complementary and alternative medicines are a fruitful source of future drugs to counteract insulin resistance. A major advantage of traditional medicine is that they have been used to treat human diseases for many years and so there is considerable knowledge concerning in vivo efficacy and safety, two of the confounding problems facing other new chemical entities. However, in most cases there is little rigorous scientific evidence proving their efficacy and the mode of action is generally not known. It has been estimated that up to one-third of patients with diabetes mellitus use some form of complementary and alternative medicine.

Bitter melon (Momordica charantia) is a popular fruit used for the treatment of diabetes and related conditions amongst the indigenous populations of Asia, South America, India and East Africa. Abundant pre-clinical studies have documented the anti-diabetic and hypoglycemic effects of Bitter melon however the precise mode of action is still unclear. This thesis aimed to evaluate the hypoglycemic activity and the probable underlying mechanisms of action of Bitter melon extract in diabetic rats by studying the changes in insulin signaling pathway in different peripheral tissues.

To achieve this aim we use rat model of type 2 diabetes mellitus which generated by injecting Wistar rats on the 5th day of their birth (n5=birth) intra-peritoneally with 100 mg/kg of STZ. All rats were followed up for 8-12 weeks to establish diabetes which was confirmed by fasting blood glucose level more than 200 mg/dl. The male diabetic rats will be divided into four groups: Group 1: the diabetic control group which received no treatment. Group 2: Bitter melon treated group. This group was divided into 4 subgroups (10 arts each) each group was treated daily with different oral doses of Bitter melon ethanolic extract (100 mg/kg,200 mg/kg,400 mg/kg and 600 mg/kg) for 30 days. Group 3: Glibenclamide treated group that was treated with glibenclamide 0.1 mg/kg (n=10) for 30 days. Also the study included a 10 healthy control rats (Group 4).

The results indicated that, the n-STZ diabetic rat model showed the typical manifestations of type 2 diabetes mellitus (T2DM) including increased weight gain, hyperglycemia, decreased insulin level and elevated HOMA-insulin resistance index compared to control rats. Also in the diabetic rats, the impaired glucose homeostasis is associated with disturbed lipid metabolism as indicated by elevated triglycerides, total cholesterol and LDL-cholesterol and decline in HDL-cholesterol.

The treatment of the diabetic rats with serial doses of ethanolic extract of bitter melon showed a dose dependent decrease in body weight and increase in fasting insulin level while the fasting blood sugar and HOMA-insulin resistance index showed dose-dependent decline with the doses from 100 to 400 mg/kg with the best results obtained with 400 mg/kg dose, the highest dose (600 mg/kg) showed significant elevated values compared to untreated diabetic rats. When comparing the efficacy of bitter melon with conventional drugs like sulfonylurea (glibenclamide) we found that bitter melon extract at dose of 400 mg/kg showed comparable improvements in glucose homeostasis parameters with glibenclamide.

The insulin resistance in diabetic rats was associated with impaired insulin signaling in liver and muscles as indicated by lowered phosphor-insulin receptor (Phospho-IR), IRS-1, PKC and Glut4. The treatment of diabetic rats with bitter melon showed a dose-dependent increase of several components of insulin signaling in liver (P-IR and IRS-1) and muscle (P-IR, IRS-1, PKC and Glut4) with the doses from 100 to 400 mg/kg while the highest dose (600mg/kg) showed less efficient effect than the lower doses. This induction effect on the expression of these components of insulin signaling at the protein level may indicate that the constituents of bitter melon may act as a positive regulators at the transcriptional, post-transcriptional and/or translational level of gene expression, however the specific constituents responsible for these induction effect need further studies.

The treatment with bitter melon show triglycerides lowering effect at low doses (100 and 200 mg/kg) while the higher doses have no significant effect. Total cholesterol showed very mild correction with bitter melon treatment. While HDL-cholesterol showed dose-dependent increase, the LDL-cholesterol showed a dose-dependent decline with bitter melon extract at doses from 100 to 400 mg/kg while highest dose showed lesser effect. Also, glibenclamide showed partial correction of lipid profile.

From the results of the present study and other related studies we can conclude that:

1- Bitter melon extract is a powerful glucose -lowering factor that play important role as anti-diabetic treatment.

2- Bitter melon produces its effect through multiple pathways:

   a- Acting as insulin secretagogue, which induce insulin secretion from β-cell

   b- Mimicking insulin action, through its constituents like p-insulin (polypeptide P) which induce insulin like action in peripheral tissue

   c- Induce peripheral tissues expression of the insulin signaling components and act as insulin sensitizer.

3- The bitter melon extract at low doses produce anti-diabetic effects equivalent to classical sulfonylurea (glibenclamide) however, high dose is less efficient and may worsen the diabetic situation.

4- Bitter melon extract have a lipid-lowering effect which partially correct dyslipidemia observed in the diabetic rats

5- Bitter melon is recommended as food supplement or pharmacological extract to treat type 2 diabetes mellitus.

7. REFERENCE

1. Alberti KGMM, Zimmet PZ for the WHO Consultation. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus. Provisional report of a WHO Consultation. Diabetic Medicine 1998; 15: 539-53.
2. Brownlee M. Biochemistry and molecular cell biology of diabetic complications. Nature 2001; 414: 813- 20
3. Fernández-Mejía C, Lazo-de-la-Vega-Monroy ML. Oxidative stress in diabetes mellitus and the role of vitamins with antioxidant actions. In: José A (ed.). Textbook of "Oxidative stress and chronic degenerative diseases- a role for antioxidants". Agricultural and Biological Sciences 2013; 1123-8.
4. Giacco F1, Brownlee M. Oxidative stress and diabetic complications.Circ Res 2010; 107: 1058-70.
5. World Health Organization. Screening for Type 2 diabetes. Report of a world health organization and international diabetes federation meeting. Geneva: World Health Organization 2003.
6. American Diabetes Association. Report of the expert committee on the diagnosis and the classification of diabetes mellitus. Diabetes Care 2009; 32: 62-7.
7. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2005; 28: 37-42.
8. Zick Y. Uncoupling insulin signalling by serine/threonine phosphorylation: a molecular basis for insulin resistance. Biochem Soc Trans 2004;32: 812- 6.
9. Weir GC1, Laybutt DR, Kaneto H, Bonner-Weir S, Sharma A. Beta-cell adaptation and decompensation during the progression of diabetes Diabetes. Diabetes. 2001 ;50 Suppl 1:154-9.
10. Leahy JL, Hirsch IB, Peterson KA, Schneider D.Targeting beta-cell function early in the course of therapy for type 2 diabetes mellitus. J Clin Endocrinol Metab 2010; 95:4206 -16.
11. Lawrence JM, Contreras R, Chen W, Sacks D."Trends in the prevalence of preexisting diabetes and gestational diabetes mellitus among a racially/ethnically diverse population of pregnant women, 1999–2005". Diabetes Care2008; 31: 899–904.
12. Saiger H, Machicao F, Fritsche A, Haring HU. Pathomechanisms of type 2 diabetes genes. Endocrine Reviews 2009; 30:557-85.
13. Wang F, Herrington M, Larssonl J, Permert J. The relationship between diabetes and pancreatic cancer. Molecular Cancer 2003; 2: 2-4.
14. Luna B, Pharm D, Feinglos MN. Drug-induced hyperglycemia. JAMA 2001; 286:1945-8.
15. Forrest JM, Fiona MT, Margaret AB, Gary FS, Frank JM, Trevor TD, et al. Congenital rubella patients 60 years later. MJA 2002; 177: 664-7.

16. D'Annunzio G, Minuto N, D'Amato E, De Toni T, Lombardo F, Pasquali L, et al. Wolfram Syndrome (Diabetes insipidus, Diabetes, optic atrophy, and deafness). Diabetes Care 2008; 31: 1743-5.

17. Shaw JE, Sicree RA, Zimmet PZ. Global estimates of the prevalence of diabetes for 2010 and 2030. Diabetes Res Clin Pract 2010; 87**:** 4–14.

18. Wild S, Roglic G, Green A, Sicree R, King H. Global Prevalence of Diabetes Estimates for the year 2000 and projections for 2030. Diabetes Care 2004; 27: 1047 – 53.

19. Colagiuri S. Diabesity: therapeutic options. Diabetes Obes Metab 2010; 12: 463–73.

20. International Expert Committee International Expert Committee report on the role of the A1C assay in the diagnosis of diabetes. Diabetes Care 2009;32:1327–34.

21. Sato KK, Hayashi T, Harita N, Yoneda T, Nakamura Y, Endo G, Kambe H. Combined measurement of fasting plasma glucose and Hemoglobin A1c (HbA1c) is effective for the prediction of type 2 diabetes: the Kansai Healthcare Study. Diabetes Care 2009; 32: 644 – 6.

22. Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J, (ed.). Diabetes mellitus. In: Harrisons Principles of Internal Medicine. McGraw-Hill. Europe 18t^{h} ed. 2011.

23. American Diabetes Association. Diagnosis and Classification of Diabetes Mellitus. Diabetes Care 2012; 35: 64–71.

24. Soltani N. Beta-Cell Function and Failure.Medicine. In:Textbook "Type 1 Diabetes". Alan P. Escher and Alice Li, (ed.). Endocrinology and Metabolism2013; 51: 115-21.

25. Gloyn AL, Weedon MN, Owen KR, Turner MJ, Knight BA, Hitman G, et al. Large - scale association studies of variants in genes encoding the pancreatic beta - cell KATP channel subunits Kir6.2 (KCNJ11)and SUR1 (ABCC8) confirm that the KCNJ11 E23K variant is associatedwith type 2 diabetes. Diabetes 2003; 52:568 – 72.

26. Nolan CJ, Damm P, Prentki M. Type 2 diabetes across generations: from pathophysiology to prevention and management. Lancet 2011; 378: 169–81.

27. O'Brien RM, Granner DK. Regulation of gene expression by insulin. Physiol Rev 1996; 76: 1109–61.

28. Yenush L, White MF. The IRS-signalling system during insulin and cytokine action. Bioessays 1997; 19: 491–500.

29. Kimball SR, Vary TC, Jefferson LS. Regulation of protein synthesis by insulin. Annu Rev Physiol 1994; 56: 321–48.

30. Randazzo PA, Morey VA, Polishook AK, Jarett L.Characterization of the growth of murine fibroblasts that express human insulin receptors. I. The effect of insulin in the absence of other growth factors. Exp Cell Res 1990; 190: 25–30.

31. Withers DJ, White M. Perspective. The insulin signaling system – a common link in the pathogenesis of type 2 diabetes. Endocrinology2000; 141: 1917–21.

32. Wu X & Garvey WT. Insulin action. In Holt RI, CocKram C, Flyvbjerg A, Goldstein BJ, (eds). Textbook of diabetes,4thedition. 2010; 102-20.

33. Boller S, Joblin BA, Xu L, Item F, Trüb T, Boschetti N, et al.From signal transduction to signal interpretation: an alternative model for the molecular function of insulin receptor substrates.Arch Physiol Biochem 2012; 118: 148-55.

34. Saltiel AR, Kahn CR Insulin signalling and the regulation of glucose and lipid metabolism. Nature 2001; 414: 799-806.

35. Paz K, Voliovitch H, Hadari YR, Roberts CT Jr, LeRoith D, Zick Y. Interaction Between the Insulin Receptor and its Downstream Effectors. Journal of Biological Chemistry1996; 271: 6998-7003.

36. Luo R.Z., Beniac DR., Fernandes A., Yip CC and Ottensmeyer F.P. Quaternary structure of the insulin-insulin receptor complex. Science 1999; 285:1077- 80.

37. Luo R.Z., Beniac DR., Yip CC, Ottensmeyer F.P. Mechanism of transmembrane signaling:insulin binding and the insulin receptor.Biochemistry 2000; 39:12103-12.

38. Hubbard SR. Crystal structure of the activated insulin receptor tyrosine kinase in complex with peptide substrate and ATP analog. Embo J 1997; 16: 5572-81.

39. Hubbard SR., Wei L., Ellis L.and Hendrickson WA. Crystal structure of the tyrosine kinase domain of the human insulin receptor. Nature 1994; 372 : 746-54.

40. Zhang BB. Insulin signaling and action: glucose, lipids, protein.Clinical Endocrinology 2007; 14: 44 – 7.

41. Bektas A, Warram JH, White MF, Krolewski AS, Doria A. Exclusion of insulin receptor substrate 2 (IRS-2) as a major locus for early-onset autosomal dominant type 2 diabetes. Diabetes 1998;48: 324-39.

42. Rhodes CJ1, White MF.Molecular insights into insulin action and secretion.Eur J Clin Invest 2002; 32: 3-13.

43. Withers DJ, Gutierrez JS, Towery H, Burks DJ, Ren JM, Previs S, et al. Disruption of IRS-2 causes type 2 diabetes in mice. Nature 1998; 391: 900 - 4.

44. Kido Y, Burks DJ, Withers D, Bruning JC, Kahn CR, White MF, et al. Tissue-specific insulin resistance in mice with mutations in the insulin receptor, IRS-1, and IRS-2. J Clin Invest 2000; 105:199-205

45. Ward CW, Lawrence MC. "Ligand-induced activation of the insulin receptor: a multi-step process involving structural changes in both the ligand and the receptor". BioEssays,2009; 31: 422–34.

46. Kaku T, Emkey R, Kriauciunas KM, and Kahn CR.. Impact of IRS-3 or IRS-4 Expression on IGF-1 Signaling Pathway in Embryonic Fibroblast Cells. Diabetes. 2000; 49: pA336.

47. Virkamäki A, Ueki K, Kahn CR. Protein-protein interactions in insulin signaling and the molecular mechanisms of insulin resistance. J Clin Invest. 1999;103:931- 43.

48. Lee YH, Giraud J, Davis RJ, White MF. cJUN N-terminal kinase (JNK) mediates feedback inhibition of the insulin signaling cascade. J Biol Chem 2002; 31: 465-78.

49. Rameh LE, Cantley LC. The role of phosphoinositide 3- kinase lipid products in cell function. J Biol Chem1999; 274: 8347 – 50.

50. Katso R, Okkenhaug K, Ahmadi K, White S, Timms J, Waterfi eld MD. Cellular function of phosphoinositide 3- kinases: implications for development, homeostasis, and cancer. Annu Rev Cell Dev Biol 2001; 17: 615 – 75.

51. Kohn AD, Summers SA, Birnbaum MJ, Roth RA. Expression of a constitutively active Akt Ser/Thr kinase in 3T3 - L1 adipocytes stimulates glucose uptake and glucose transporter 4 translocation. J Biol Chem 1996 ; 271 : 31372 – 8.

52. Frame S, Zheleva D. Targeting glycogen synthase kinase - 3 in insulin signalling. Expert Opin Ther Targets 2006; 10: 429 – 44.

53. Sano H, Kane S, Sano E, M î inea CP, Asara JM, Lane WS, et al. Insulin - stimulated phosphorylation of a Rab GTPase - activating protein regulates GLUT4 translocation. J Biol Chem 2003; 278: 14599 – 602.

54. Mellor H, Parker PJ. "The extended protein kinase C superfamily". Biochem. J 1998; 332: 281–92.

55. Farese RV. Function and dysfunction of aPKC isoforms for glucose transport in insulin - sensitive and insulin - resistant states. Am J Physiol Endocrinol Metab 2002; 283: 1 – 11.

56. Liu LZ, Zhao HL, Zuo J, Ho SK, Chan JC, Meng Y, et al. Protein kinase C zeta mediates insulin - induced glucose transport through actin remodeling in L6 muscle cells. Mol Biol Cell 2006 ; 17 : 2322 –30.

57. Uldry M, Thorens B. The SLC2 family of facilitated hexose and polyol transporters. Pflügers Arch 2004; 447: 480 – 9.

58. Joost HG, Bell GI, Best JD, Birnbaum MJ, Charron MJ, Chen YT, et al. Nomenclature of the GLUT/SLC2A family of sugar/polyol transport facilitators. Am. J. Physiol. Endocrinol. Metab. 2002; 282: 974 – 6.

59. Thorens B and Mueckler M. Glucose transporters in the 21st century. Am. J.Physiol. Endocrinol. Metab 2010; 298: 141–5.

60. Yu S, Zhao T, Guo M, Fang H, Ma J, Ding A, et al. Hypoxic preconditioning up-regulates glucose transport activity and glucose transporter (GLUT1 and GLUT3) gene expression after acute anoxic exposure in the cultured rat hippocampal neurons and astrocytes. Brain Res 2008; 1211: 22– 9.

61. Kellett GL, Brot-Laroche E, Mace OJ, Leturque A. Sugar absorption in the intestine: the role of GLUT2. Annu Rev Nutr 2008; 28: 35–54.

62. Simpson IA, Dwyer D, Malide D, Moley KH, Travis A, Vannucci SJ. The facilitative glucose transporter GLUT3: 20 years of distinction. Am. J. Physio.l Endocrinol. Metab 2008; 295: 242–53.

63. Watson RT, Pessin JE. Subcellular compartmentalization and trafficking of the insulin - responsive glucose transporter, GLUT4. Exp Cell Res 2001; 271: 75 – 83.

64. Al-Hasani H, Kunamneni RK, Dawson K, Hinck CS, Muller- Wieland D, Cushman SW. Roles of the N- and C-termini of GLUT4 in endocytosis. J Cell Sci 2002; 115: 131–40.

65. Palacios S, Lalioti V, Martinez-Arca S, Chattopadhyay S, Sandoval IV. Recycling of the insulin-sensitive glucose transporter GLUT4. Access of surface internalized GLUT4 molecules to the perinuclear storage compartment is mediated by the Phe5-Gln6- Gln7-Ile8 motif. J. Biol. Chem. 2001; 276: 3371–83.

66. Melvin DR, Marsh BJ, Walmsley AR, James DE, Gould GW. Analysis of amino and carboxy terminal GLUT-4 targeting motifs in 3T3–L1 adipocytes using an endosomal ablation technique. Biochemistry. 1999; 38: 1456–62.

67. Seatter M J., De La Rue SA., Porter LM., Gould GW. QLS Motif in Transmembrane Helix VII of the Glucose Transporter Family Interacts with the C-1 Position of D-Glucose and Is Involved in Substrate Selection at the Exofacial Binding Site. Biochemistry 1998; 37: 1322 -6.

68. Röckl KS, Witczak CA, Goodyear LJ. Signaling mechanisms in skeletal muscle: acute responses and chronic adaptations to exercise.IUBMB Life 2008; 60: 145-53.

69. Buhl ES, Jessen N, Schmitz O, Pedersen SB, Pedersen O, Holman GD, et al. Chronic treatment with 5-aminoimidazole-4-carboxamide-1-beta-Dribofuranoside increases insulin-stimulated glucose uptake and GLUT4 translocation in rat skeletal muscles in a fiber type-specific manner. Diabetes 2001; 50: 12-7.

70. Fernandez - Novell JM, Bellido D, Vilaro S, Guinovart JJ. Glucose induces the translocation of glycogen synthase to the cell cortex in rat hepatocytes. Biochem J 1997; 321: 227 – 31.

71. DeFronzo RA, Tripathy D. Skeletal muscle insulin resistance is the primary defect in type 2 diabetes. Diabetes Care 2009; 32:157-63.

72. Blot V, McGraw TE. GLUT4 is internalized by a cholesterol- dependent nystatin - sensitive mechanism inhibited by insulin. Embo J 2006; 25: 5648 –58.

73. Ros - Baro A, Lopez - Iglesias C, Peiro S, Bellido D, Palacin M, Zorzano A, et al. Lipid rafts are required for GLUT4 internalization in adipose cells. Proc Natl Acad Sci U S A 2001; 98: 12050 –5.

74. Gaidhu MP1, Ceddia RB. The role of adenosine monophosphate kinase in remodeling white adipose tissue metabolism. Exerc Sport Sci Rev 2011; 39: 102-8.

75. Shimano H, Yahagi N, Amemiya- Kudo M, Hasty AH, Osuga J, Tamura Y, et al. Sterol regulatory element - binding protein - 1 as a key transcription factor for nutritional induction of lipogenic enzyme genes. J Biol Chem 1999; 274: 35832 – 9.

76. Londos C, Brasaemle DL, Schultz CJ, Adler - Wailes DC, Levin DM, Kimmel AR, et al. On the control of lipolysis in adipocytes. Ann N Y Acad Sci 1999; 892: 155 – 68.

77. Holm C. Molecular mechanisms regulating hormone - sensitive lipase and lipolysis. Biochem Soc Trans 2003; 31: 1120 – 4.

78. Yeaman SJ. Hormone- sensitive lipase: new roles for an old enzyme. Biochem J 2004; 379: 11 – 22.

79. Blanchette- Mackie EJ, Dwyer NK, Barber T, Coxey RA, Takeda T, Rondinone CM, et al. Perilipin is located on the surface layer of intracellular lipid droplets in adipocytes. J Lipid Res 1995; 36: 1211 –26.

80. Fricke K, Heitland A, Maronde E. Cooperative activation of lipolysis by protein kinase A and protein kinase C pathways in 3T3 - L1 adipocytes. Endocrinology 2004; 145: 4940 –7.

81. Tansey JT, Sztalryd C, Gruia - Gray J, Roush DL, Zee JV, Gavrilova O, et al. Perilipin ablation results in a lean mouse with aberrant adipocyte lipolysis, enhanced leptin production, and resistance to diet - induced obesity. Proc Natl Acad Sci U S A 2001; 98: 6494 – 9.

82. Arimura N, Horiba T, Imagawa M, Shimizu M, Sato R. The peroxisome proliferator - activated receptor gamma regulates expression of the perilipin gene in adipocytes. J Biol Chem 2004; 279: 10070 – 6.

83. Wroblewski M, Gottsater A, Lindgarde F, Fernlund P, Sundkvist G. Gender, autoantibodies, and obesity in newly diagnosed diabetic patients aged 40 – 75 years. Diabetes Care 1998; 21: 250 – 5.

84. Alsahli M & Gerich JE. Abnormalities of Insulin Secretion and β - Cell Defects in Type 2 Diabetes. In: Holt RI, CocKram C, Flyvbjerg A, Goldstein BJ, eds. Textbook of diabetes,4thedition 2010; 160-73.

85. Gerich J. The genetic basis of type 2 diabetes mellitus: impaired insulin secretion versus impaired insulin sensitivity. Endocr Rev 1998; 19: 491 – 503.

86. Hamman R. Genetic and environmental determinants of noninsulin dependent diabetes mellitus (NIDDM). Diabetes Metab Rev 1992; 8: 287 – 338.

87. Reaven G. Pathophysiology of insulin resistance in human disease. Physiol Rev 1995; 75: 473 – 86.

88. DeFronzo R.Pathogenesis of type 2 diabetes mellitus. Med Clin North Am 2004; 88:787-835.

89. Olefsky J, Nolan J. Insulin resistance and non- insulin- dependent diabetes mellitus: cellular and molecular mechanisms. Am J Clin Nutr 1995; 61: 980 – 6.

90. Kahn S. The importance of β - cell failure in the development and progression of type 2 diabetes. J Clin Endocrinol Metab 2001; 86: 4047 – 58.

91. Pratley R, Weyer C. The role of impaired early insulin secretion in the pathogenesis of type II diabetes mellitus. Diabetologia 2001; 44: 929 – 45.

92. Polonsky K, Sturis J, Bell G. Non insulin-dependent diabetes mellitus: a genetically programmed failure of the beta cell to compensate for insulin resistance. N Engl J Med 1996; 334: 777 – 83.

93. Barnes BR, Ryder JW, Steiler TL, Fryer LG, Carling D, Zierath JR. Isoform specific regulation of 5' AMP-activated protein kinase in skeletal muscle from obese Zucker rats in response to contraction. Diabetes 2002; 51: 2703 - 8.

94. Pirola L, Johnston AM, Van Obberghen E. Modulation of insulin action. Diabetologia 2004; 47: 170-84.

95. Reaven GM. Insulin resistance, the insulin resistance syndrome, and cardiovascular disease. Panminerva Med 2005; 47: 201-10.

96. King MW. Insulin activities. 1996–2013 themedicalbiochemistrypage.org,

97. Wallace TM, Matthews DR. The drug treatment of type 2 diabetes. In: Pickup JC, Williams G, eds. Textbook of Diabetes, 3rd edn. Oxford: Blackwell 2003; 45: 1 – 18.

98. Krentz AJ, Bailey CJ. Type 2 Diabetes in Practice, 2nd edn. London:Royal Society of Medicine Press, 2005.

99. Vuksan V, John L. Sievenpiper. Herbal remedies in the management of diabetes: Lessons learned from the study of ginseng. Nutrition, Metabolism & Cardiovascular Diseases 2005; 15: 149-60.

100. Black C, Donnelly P, McIntyre L, Royle PL, Shepherd JP, Thomas S. Meglitinide analogues for type 2 diabetes mellitus. Cochrane Database Syst Rev 1, 2007; 46-54.

101. Saenz A, Fernandez-Esteban I, Mataix A, Ausejo M, Roque M, Moher D. Metformin monotherapy for type 2 diabetes mellitus. Cochrane Database Syst Rev 3, 2005; 29-66.

102. Salpeter S, Greyber E, Pasternak G, Salpeter E. Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus. Cochrane Database Syst Rev, 2006; 4: 29-67.

103. Bailey CJ. Hypoglycaemic, antihyperglycaemic and antidiabetic drugs. Diabet Med 1992; 9: 492 – 3.

104. Bailey CJ. Drugs on the horizon for diabesity. Curr Diabetes Rep2005; 5: 353 – 9.

105. Bailey CJ. Treating insulin resistance: future prospects. Diabetes Vasc Dis Res 2007; 4: 20 – 31.

106. Bailey CJ, Krentz AJ. Oral Antidiabetic Agents. In: Holt RI, CocKram C, Flyvbjerg A, Goldstein BJ, eds. Textbook of diabetes,4th edition. 2010; 452-77.

107. World Health Organization. Model List of Essential Medicines,15th edition. Retrieved on 2007; 21: 11-9.

108. Riddle MC. "Editorial: sulfonylureas differ in effects on ischemic preconditioning--is it time to retire glyburide?". J Clin Endocrinol Metab 2003; 88: 528–30.

109. Serrano-Martín X, Payares G. Glibenclamide, a Blocker of K+ATP Channels, Shows Antileishmanial Activity in Experimental Murine Cutaneous Leishmaniasis. Antimicrob. Agents Chemother 2006; 50: 4214– 6.

110. Monami M, Luzzi C, Lamanna C, Chiasserini V, Addante F, Desideri CM, et al. Three-year mortality in diabetic patients treated with different combinations of insulin secretagogues and metformin. Diabetes Metab Res Rev 2006; 22: 477 – 82.

111. Prasad CN. Isolation and characterization of modulators of Glut4 translocation from medicinal plants. Amritia school of biotechnology 2011; 21: 17-9.

112. Yibchok-anun S, Adisakwattana S, Yao CY, Sangvanich P, Roengsumran S. Slow acting protein extract from fruit pulp of Momordica charantia with insulin secretagogue and insulinomimetic activities. Biol Pharm Bull 2006; 29: 1126 - 31.

113. Roffey BW, Atwal AS, Johns T, Kubow S. Water extracts from Momordica charantia increase glucose uptake and adiponectin secretion in 3T3-L1 adipose cells. J Ethnopharmacol 2007; 30: 77-84.

114. Mahomoodally MF, Gurib-Fakim A, Subratty AH. Effect of exogenous ATP on Momordica charantia Linn. (Cucurbitaceae) induced inhibition of D-glucose, L tyrosine and fluid transport across rat everted intestinal sacs in vitro. J Ethnopharmacol 2007; 21: 257 - 63.

115. Fernandes NP, Lagishetty CV, Panda VS, Naik SR. An experimental evaluation of the antidiabetic and antilipidemic properties of a standardized Momordica charantia fruit extract. BMC Complement Altern Med 2007; 24: 7-29.

116. Kumar R, Balaji S, Uma TS, Sehgal PK. Fruit extracts of Momordica charantia potentiate glucose uptake and up-regulate Glut-4, PPAR gamma and PI3K. J Ethnopharmacol 2009; 126: 533 – 7.

117. Tan MJ, Ye JM, Turner N, Behrens CH, Ke CQ, Tang CP, et al. Antidiabetic activities of triterpenoids isolated from Bitter Melon associated with activation of the AMPK pathway. Chem. Biol 2008; 15: 263–73.

118. Leung L, Birtwhistle R, Kotecha J, Hannah S, Cuthbertson S. Anti-diabetic and hypoglycaemic effects of Momordica charantia (bitter melon): a mini review. Br J Nutr 2009; 102: 1703-8.

119. Plant resources of tropical africa database. available at: http://database. prota.org/ search.htm, 13; 2006.

120. Reyes MEC, Gildemacher BH, Jansen GJ. MomordicaL. In: Siemonsma JS, Piluek K, editors.Plant Resources of South-East Asia. No. 8: Vegetables.bogor, indonesia: Prosea 1994; 100: 415 – 21.

121. Yeh GY, Eisenber DM, Kaptchuk TJ, Phillips RS. Systematic review of herbs and dietary supplements for glycemic control in diabetes. Diabetes Care 2003; 26: 1277– 94.

122. Beloin N, Gbeassor M, Akpagana K, Hudson J, de Soussa K, Koumaglo K, et al. Ethnomedicinal uses of Momordicacharantia (Cucurbitaceae) in Togo and relation to its phytochemistry and biological activity. J Ethnopharmacol 2005; 96: 49-55.

123. Virdi J, Sivakami S, Shahani S, Suthar AC, Banavalikar MM, Biyani MK. Anti hyperglycemic effects of three extracts from Momordica charantia. J Ethnopharmacol. 2003; 88: 107-11.

124. Shetty AK1, Kumar GS, Sambaiah K, Salimath PV. "Effect of bitter gourd (Momordica charantia) on glycaemic status in streptozotocin induced diabetic rats". Plant Foods Hum Nutr 2005; 60: 109–12.

125. Kumar DS, Sharathnath KV, Yogeswaran P, Harani A, Sudhakar K, Banji D. A Medicinal potency of Momordica charantia. International Journal of Pharmaceutical Sciences Review and Research 2010; 1: 95-100.

126. Khan A, Anderson RA. Insulin Potentiating Factor (IPF) Present in Foods, Species and Natural Products. Pakistan Journal of Nutrition 2003; 2: 254-7

127. Krawinkel MB, Keding GB. Bitter gourd (Momordica Charantia): A dietary approach to hyperglycemia. Nutr Rev 2006; 64: 331-7.

128. Cummings E, Hundal HS, Wackerhage H. Momordica charantia fruit juice stimulates glucose and amino acid uptakes in L6 myotubes. Mol Cell Biochem. 2004; 261: 99 – 104.

129. Arulmozhi DK, Veeranjaneulu A, Bodhankar SL. Neonatal streptozotocin-induced rat model of type 2 diabetes mellitus: A glance. Indian J Pharamacol 2004; 36: 217-21.

130. El-Bassiouni EA, Helmy MH, Abou Rawash N, EL-Zoghby SM, Kamel MA-N, Abou Raya AN. Embryopathy in experimental diabetic gestation: Assessment of oxidative stress and antioxidant defense. Brit J Biomed Sci 2005; 62:71-6.

131. Saad Mohamed El-Said and Ali S. Al-Barak. Extraction of Insulin like Compounds from Bitter Melon Plants. American Journal of Drug Discovery and Development 2011; 1: 1-7.

132. Weyer C, Hanson RL, Tataranni PA, Bogardus C, Pratley RE. A high fasting plasma insulin concentration predicts type 2 diabetes independent of insulin resistance. Diabetes. 2000; 76: 2094–101

133. Tietz NW. Clinical chemistry and molecular diagnostics.4th edition. WB Saunders Company, Philadelphia 2006, pp. 902 -5 (glucose), 887 (insulin), 891 (insulin resistance).

134. Caumo A, Perseghin G, Brunani A, Luzi L. New insights on the simultaneous assessment of insulin sensitivity and Beta-cell function with the HOMA2 method. Diabetes Care. 2006; 29:2733-4.

135. Burtis C, Ashwood ER, Bruns DE. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 4th edition. Elsevier Saunders Company. St Louis. 2006, pp. 938-40 (Lipid profile, TG).

136. Burtis C, Ashwood ER, Bruns DE. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 4th edition. Elsevier Saunders Company. St Louis. 2006, pp. 945-47. (Lipid profile, cholesterol).

137. Burtis C, Ashwood ER, Bruns DE. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 4th edition. Elsevier Saunders Company. St Louis. 2006, pp. 952-55 (HDL & LDL-cholesterol).

138. Lowry OH, Rosebrough NJ, Farr AL, Randall RJ. Protein measurements with Folin-phenol reagent. J. Biol. Chem. 1951; 193: 265-70.

139. Ottensmeyer FP, Beniac DR, Luo RZ, Yip CC. Mechanism of transmembrane signaling: insulin binding and the insulin receptor. Biochemistry 2000; 39:12103-12.

140. Wang Y, Nishina PM, Naggert JK. Degradation of IRS1 leads to impaired glucose uptake in adipose tissue of the type 2 diabetes mouse model. J Endocrinol 2009; 203: 65-74.

141. Wetsel WC, Khan WA, Merchenthaler I, Rivera H, Halpern AE, Phung HM, et al. Tissue and cellular distribution of the extended family of protein kinase C isoenzymes. JCB 1992; 117: 121-33.

142. Koehn FE, Carter GT. The evolving role of natural products in drug discovery. Nat. Rev. Drug Discov.2005; 4: 206–20.

143. Rizvi SI, Mishra N.Traditional Indian medicines used for the management of diabetes mellitus. J Diabetes Res 2013; 2013: 712092.

144. Hays NP, Galassetti PR, Coker RH.Prevention and treatment of type 2 diabetes: current role of lifestyle, natural product, and pharmacological interventions.Pharmacol Ther. 2008; 118: 181-91

145. Portha B, Blondel O, Serradas P. The rat models of non-insulin dependent diabetes induced by neonatal streptozotocin. Diabetes Metab 1989; 15: 61–75.

146. Grover JK, Yadav S, Vats V. Medicinal plants of India with anti-diabetic potential. J Ethnopharmacol 2002; 81: 81–100.

147. Chandrasekar B, Mukherjee B, Mukherjee SK. Blood sugar lowering potentiality of selected Cucurbitaceae plants of Indian origin. Indian J Med Res1989; 90: 300–5.

148. Shibib BA, Khan LA, Rahman R. Hypoglycemic activity of Coccinia indica and Momordica charantia in diabetic rats: depression of the hepatic gluconeogenic enzymes glucose-6-phosphatase and fructose-1,6-bisphosphatase and elevation of both liver and red-cell shunt enzyme glucose-6-phosphate dehydrogenase. Biochem J 1993; 292(Part 1) : 267–70.

149. Yuan XQ, Gu XH, Tang J, Wasswa J. Hypoglycemic effects of semipurified peptides from Momordica charantia. J Food Biochem. 2008; 32: 107 – 21.

150. Hui H, Tang G, Liang V. Hypoglycemic herbs and their mechanisms of action. Chinese Medicine. 2009; 4:11.

151. Toshihiro M, Chisa I, Naoki I, Motoshi K, Rae PS, Ikukatsu S. Hypoglycemic activity of the fruit of the *Momordica charantia* in type 2 diabetic mice. J Nutr Sci Vitaminol. 2001; 47: 340-4.

152. Subratty AH, Gurib-Fakim A, Mahmoodally F. Bitter melon: an exotic vegetable with medicinal values. JNFS 2005; 35:143-7.

153. Ayoub SM, Rao S, Byregowda SM, Satyanarayana ML, Bhat N, Shridhar PB. Evaluation of Hypoglycemic Effect of Momordica charantia Extract in Distilled Water in Streptozotocin-Diabetic Rats. Braz J Vet Pathol 2013; 6: 56 - 64

154. Senanayake GVK, Maruyama M, Sakono M, Fukuda N, Morishita T, Yukizaki C, et al. The effects of bitter melon (Momordica charantia) extracts on serum and liver lipid parameters in hamsters fed cholesterol-free and cholesterolenriched diets. Journal of Nutritional Science and Vitaminology 2004; 50: 253 - 7.

155. Rahmana I, Malika SA, Bashirb M, Khanc R, Iqbald M. Serum sialic acid changes in non-insulin-dependant diabetes mellitus (NIDDM) patients following bitter melon (Momordica charantia) and rosiglitazone (Avandia) treatment. Phytomedicine 2009; 16: 401–5.

156. Bakare RI, Magbagbeola OA, Akinwande AI, Okunowo OW. Nutritional and chemical evaluation of Momordica charantia. J Med Plant Res 2010; 4: 2189 - 93.

157. Snee LS, Nerurkar VR, Dooley DA, Efird JT, Shovic AC, Nerurkar PV. Strategies to improve palatability and increase consumption intentions for Momordica charantia (bitter melon): A vegetable commonly used for diabetes management. Nutr J 2011; 10: 78.

158. Mahomoodally MF, Subratty AH, Gurib-Fakim A, Choudhary MI, Nahar Khan S. Traditional medicinal herbs and food plants have the potential to inhibit key carbohydrate hydrolyzing enzymes invitro and reduce postprandial blood glucose peaks in vivo.Scientific World Journal. 2012; 2012: 285284.

159. Ahmed I, Adeghate E, Cummings E, Sharma AK, Singh J. Beneficial effects and mechanism of action of Momordica charantia juice in the treatment of streptozotocin-induced diabetes mellitus in rat. Mol Cell Biochem 2004; 261: 63–70.

160. Chaturvedi P. Antidiabetic potentials of Momordica charantia: multiple mechanisms behind the effects. J Med Food. 2012; 15:101-7.

161. Kumar Shetty A, Suresh Kumar G, Veerayya Salimath P. Bitter gourd (Momordica charantia) modulates activities of intestinal and renal disaccharidases in streptozotocin-induced diabetic rats. Mol Nutr Food Res 2005; 49: 791– 96.

162. Mohiti-Asli M, Shivazad M, Zaghari M, Aminzadeh S, Rezaian M, Mateos GG. Dietary fibers and crude protein content alleviate hepatic fat deposition and obesity in broiler breeder hens 2012; 91: 3107-14.

163. Nandini CD, Sambaiah K, Salimath PV. Dietary fibers ameliorate decreased synthesis of heparan sulphate in streptozotocin induced diabetic rats. J Nutr Biochem 2003; 14: 203–10.

164. Singh N, Gupta M, Sirohi P, Varsha. Effects of alcoholic extract of Momordica charantia (Linn.) whole fruit powder on the pancreatic islets of alloxan diabetic albino rats. J Environ Biol 2008; 29(1):101- 6.

165. Jeong J, Lee S, Hue J, Lee K, Nam SY, Yun YW, et al. Effect of bitter melon (Momordica Charantia) on antidiabetic activity in C57BL/6J db/db mice. Korean J Vet Res 2008; 48: 327- 36.

166. Garau C, Cummings E, David A. Phoenix, Jaipaul Singh. Beneficial effect and mechanism of action of Momordica charantia in the treatment of diabetes mellitus: a mini review. Am J Health Syst Pharm 2003; 60: 356-9.

167. Singh N, Gupta M. Regeneration of beta cells of pancrease of alloxan diabetic rats by acetone extract of M. charantia fruits. Indian J. Exp. Biol. 2007; 45:1055 - 62.

168. Parmar K, Patel S, Patel J, Patel B, Patel MB. Effects of bitter gourd (Momordica charantia) fruit juice on glucose tolerance and lipid profile in type-II diabetic rats. Int J Drug Dev Res 2011; 3: 139-46.

169. Xiang L, Huang X, Chen L, Rao P, Ke L. The reparative effects of Momordica charantia Linn. extract on HIT-T15 pancreatic beta cells. Asia Pac J Clin Nutr. 2007; 16: 249 - 52.

170. Vashum KP, McEvoy M, Milton AH, Islam MR, Hancock S, Attia J. Is serum zinc associated with pancreatic beta cell function and insulin sensitivity in pre-diabetic and normal individuals? Findings from the Hunter Community Study. PLoS One. 2014; 9: 83944.

171. Henquin JC, Meissner HP. Cyclic adenosine monophosphate differently affects the response of mouse pancreatic beta - cells to various amino acids. J Physiol 1986 ; 381 : 77 – 93.

172. Soltani N, Qiu H, Aleksic M, Glinka Y, Zhao F, Liu R, et al. GABA exerts protective and regenerative effects on islet beta cells and reverses diabetes.Proc Natl Acad Sci U S A 2011; 108: 11692-7

173. Dans AM, Villarruz MV, Jimeno CA, Javelosa MA, Chua J, Bautista R, et al. The effect of Momordica charantia capsule preparation on glycemic control in type 2 diabetes mellitus needs further studies. Med Monatsschr Pharm. 2007; 30: 131-7.

174. Wang ZQ, Zhang XH, Yu Y, Poulev A, Ribnicky D, Floyd ZE, et al. Bioactives from bitter melon enhance insulin signaling and modulate acyl carnitine content in skeletal muscle in high-fat diet-fed mice. J Nutr Biochem 2011; 22: 1064-73.

175. Shih CC, Lin CH, Lin WL, Wu JB. Momordica charantia extract on insulin resistance and the skeletal muscle GLUT4 protein in fructose-fed rats. J Ethnopharmacol. 2009; 123: 82–90.

176. Efird JT, Choi YM, Davies SW, Mehra S, Anderson EJ, Katunga LA et al. Potential for improved glycemic control with dietary Momordica charantia in patients with insulin resistance and pre-diabetes.Int J Environ Res Public Health 2014; 11: 2328-45.

177. Huang S, Czech MP. The GLUT4 glucose transporter. Cell Metab 2007; 5: 237–52.

178. Tayyab F, Lal SS, Mishra M, Kumar U. A review: Medicinal plants and its impact on diabetes. World J Pharm Res 2012; 1: 1019 - 46.

179. Paul A, Raychaudhuri SS. Medicinal uses and molecular identification of two Momordica charantia varieties - a review. E J Bio 2010; 6: 43-51.

180. Blum A, Loerz C, Martin HJ, Staab-Weijnitz CA, Maser E. Momordica charantia extract, a herbal remedy for type 2 diabetes, contains a specific 11β-hydroxysteroid dehydrogenase type 1 inhibitor.J Steroid Biochem Mol Biol 2012; 128: 51-5.

181. Blum A, Maser E. Enzymology and molecular biology of glucocorticoid metabolism in humans, Prog. Nucleic Acid Res. Mol. Biol 2003; 75: 173–216.

182. Maser E, Völker B, Friebertshäuser J. 11 Beta-hydroxysteroid dehydrogenase type 1 from human liver: dimerization and enzyme cooperativity support its postulated role as glucocorticoid reductase. Biochemistry 2002; 41: 2459 – 65.

183. Wamil M, Seckl JR, Inhibition of 11beta-hydroxysteroid dehydrogenase type 1 as a promising therapeutic target, Drug Discov 2007; 12: 504–20.

184. Staab CA, Maser E. 11Beta-Hydroxysteroid dehydrogenase type 1 is an important regulator at the interface of obesity and inflammation, J Steroid Biochem. Mol Biol 2010; 119: 56 - 72.

185. Chahil TJ, Ginsberg HN: Diabetic dyslipidemia. Endocrinol Metab Clin North Am 2006; 35: 491–510

186. Nerurkar PV, Lee YK, Adeli K, Nerurkar VR. Momordica charantia (bitter melon) improves hepatic insulin signaling. FASEB Journal 2008; 22: 948- 62.

187. Komolafe OA, Ofusori DA, Adewole OS, Fakunle JB. Effects of Momordica charantia on serum lipid profile, serum protein levels and selected markers of cardiovascular damage in diabetic rats. British Journal of Pharmaceutical Research 2014; 4: 429-42.

188. Oishi Y, Sakamoto T, Udagawa H, et al. Inhibition of increases in blood glucose and serum neutral fat by Momordica charantia saponin fraction. Biosci Biotechnol Biochem 2007; 71: 735-40.

189. Chaturvedi P. Role of Momordica charantia in maintaining the normal levels of lipids and glucose in diabetic rats fed a high-fat and low-carbohydrate diet. Br J Biomed Sci 2005; 62: 124 -6.

190. Chaturvedi P, George S, Milinganyo M, Tripathi YB. Effect of Momordica charantia on lipid profile and oral glucose tolerance in diabetic rats. Phytother Res 2004;18: 954 -6.

191. Ahmed I, Lakhani MS, Gillett M. Hypotriglyceridemic and hypocholesterolemic effects of anti-diabetic Momordica charantia (karela) fruit extract in streptozotocin-induced diabetic rats. Diabetes Res Clin Pract 2001; 51: 155-61.

192. Basch WE, Gabardi S, Ulbricht C. Bitter melon (Momordica charantia): A review of efficacy and safety. Am J Health Syst Pharm 2003; 60: 356 – 9.

Table: **Weight (gm) in healthy control and diabetic groups with and without treatments.**

Weight (gm)	Healthy control	Diabetic Groups					
		No Tx	Tx Glibin	Tx 100.0	Tx 200.0	Tx 400.0	Tx 600.0
1	180.0	191.0	232.0	210.0	198.0	205.0	209.0
2	235.0	240.0	180.0	214.0	263.0	260.0	231.0
3	250.0	290.0	206.0	228.0	286.0	180.0	202.0
4	190.0	215.5	193.0	250.0	243.0	221.0	214.0
5	217.0	265.0	202.8	288.0	213.0	269.0	208.3
6	177.0	252.7	197.9	235.0	173.0	227.0	208.1
7	206.0	240.2	200.3	235.0	268.0	248.0	208.1
8	207.9	260.0	199.1	245.0	234.9	237.5	209.6
9	206.9	190.0	199.7	244.0	251.4	242.8	208.5
10	207.4	291.0	199.4	230.0	243.1	240.1	208.6
Mean ± SD	207.7±22.7	243.5±36.0	201.0±13.0	237.9±21.8	237.3±34.2	233.0±26.2	210.7±7.7

Table: The levels of FBS (mg/dl) in healthy control and diabetic groups with and without treatments.

FBS (mg/dl)	Healthy control	Diabetic Groups					
		No Tx	Tx Glibin	Tx 100.0	Tx 200.0	Tx 400.0	Tx 600.0
1	85.0	223.0	112.0	149.0	169.6	123.0	160.5
2	106.0	197.0	110.0	139.0	118.5	117.0	195.5
3	93.0	257.0	122.0	136.0	109.6	98.0	171.5
4	89.0	210.0	126.5	141.3	89.6	163.0	167.0
5	95.0	227.0	105.0	138.8	103.2	112.0	173.6
6	93.0	233.5	126.0	138.7	223.0	78.4	176.9
7	100.0	230.5	104.0	139.6	139.0	81.0	172.3
8	94.4	230.0	124.0	139.0	177.0	110.3	172.4
9	97.0	197.0	139.0	140.2	121.0	95.7	173.8
10	96.0	255.0	115.0	139.6	138.9	103.0	173.9
Mean ± SD	94.8± 5.7	226.0± 20.7	118.4 ± 11.1	140.1± 3.4	138.9±40.5	108.1± 24.1	173.7± 8.9

Table: The levels of Insulin (ug/mg protein) in healthy control and diabetic groups with and without treatments.

Insulin (ug/mg protein)	Healthy control	Diabetic Groups					
		No Tx	Tx Glibin	Tx 100.0	Tx 200.0	Tx 400.0	Tx 600.0
1	0.4	0.3	0.6	0.3	0.3	0.3	0.4
2	0.3	0.3	0.4	0.2	0.2	0.3	0.7
3	0.7	0.2	0.4	0.2	0.2	0.4	0.6
4	0.2	0.2	0.5	0.4	0.4	0.9	0.5
5	0.5	0.3	0.4	0.6	0.6	0.4	0.7
6	0.4	0.3	0.6	0.3	0.3	0.5	0.4
7	0.5	0.3	0.4	0.5	0.5	0.4	0.8
8	0.3	0.3	0.6	0.4	0.4	0.4	0.5
9	0.4	0.2	0.4	0.4	0.4	0.4	0.5
10	0.3	0.3	0.6	0.4	0.4	0.4	0.4
Mean ± SD	0.40±0.13	0.25 ± 0.02	0.46 ± 0.10	0.32 ± 0.09	0.38 ± 0.11	0.44 ± 0.17	0.56 ± 0.16

Table: The levels of HOMA-IR in healthy control and diabetic groups with and without treatments.

HOMA-IR	Healthy control	Diabetic Groups					
		No Tx	Tx Glibin	Tx 100.0	Tx 200.0	Tx 400.0	Tx 600.0
1	2.0	3.7	3.6	2.4	2.6	2.1	3.7
2	2.1	2.9	2.3	2.3	1.6	2.0	8.5
3	3.8	3.7	2.6	1.4	1.5	2.4	6.5
4	1.3	2.7	3.8	4.4	2.3	8.6	4.9
5	2.9	3.5	2.4	2.8	3.5	2.4	7.6
6	1.9	3.7	4.1	2.6	4.6	2.1	4.2
7	2.8	3.4	2.3	2.7	3.8	2.0	8.6
8	1.7	3.7	4.1	2.7	4.2	2.8	5.1
9	2.2	2.4	3.0	2.7	3.1	2.4	5.1
10	2.0	4.2	3.8	2.7	3.4	2.6	4.1
Mean ± SD	2.27± 0.72	3.40 ± 0.54	3.23 ± 0.77	2.68 ± 0.72	3.07 ± 1.05	2.94 ± 2.01	5.84 ± 1.85

Table: The Levels of Triglycerides (mg/dl) in healthy control and diabetic groups without and with Treatments.

T.G (mg/dl.)	Healthy control	Diabetic Groups					
		No Tx	Tx Glibin	Tx 100.0	Tx 200.0	Tx 400.0	Tx 600.0
1	43.6	112.0	59.4	75.3	133.0	105.4	115.0
2	29.8	143.0	87.0	88.1	74.1	105.9	83.0
3	35.5	122.0	73.2	159.5	158.1	82.3	135.0
4	28.3	127.0	80.1	81.0	23.3	84.0	118.0
5	29.1	116.0	76.7	66.0	42.4	92.0	90.3
6	29.8	131.0	78.4	57.0	108.0	66.1	99.1
7	49.0	98.0	77.5	68.1	95.0	108.7	103.1
8	35.0	88.0	77.9	48.3	59.5	132.1	95.1
9	42.0	112.0	77.7	80.4	47.9	120.4	96.9
10	38.5	131.0	77.8	64.4	53.7	126.2	98.5
Mean ± SD	36.1±7.1	118.0±16.5	76.6±7.0	78.8±30.8	79.5 ± 43.1	102.3±21.1	103.4±15.2

Table: The Levels of Total Cholesterol (mg/dl) in healthy control and diabetic groups without and with Treatments.

Total Cholesterol (mg/dl.)	Healthy control	Diabetic Groups					
		No Tx	Tx Glibin	Tx 100.0	Tx 200.0	Tx 400.0	Tx 600.0
1	158.0	173.0	142.3	200.0	191.0	195.5	138.0
2	135.5	180.0	164.3	202.0	226.0	212.0	191.0
3	147.0	159.0	153.0	192.0	127.0	201.0	141.0
4	145.5	189.0	159.0	144.2	149.0	159.0	157.0
5	138.0	194.0	156.5	175.0	188.0	156.0	156.0
6	150.0	188.0	155.0	141.0	193.0	144.5	161.0
7	115.0	197.0	155.0	185.0	170.5	174.0	154.0
8	135.0	185.0	160.0	153.0	165.0	177.0	157.0
9	149.0	187.0	156.0	174.0	166.0	176.0	157.0
10	148.0	205.0	156.0	164.0	184.0	177.0	158.0
Mean ± SD	142.1±11.9	185.7±12.9	155.7±5.7	173.0±22.1	176.0±27.1	177.2±21.0	157.0±14.1

Table: The Levels of LDL- Cholesterol (mg/dl) in healthy control and diabetic groups without and with Treatments.

LDL-Cholesterol (mg/dl.)	Healthy control	Diabetic Groups					
		No Tx	Tx Glibin	Tx 100.0	Tx 200.0	Tx 400.0	Tx 600.0
1	100.3	126.0	113.2	132.6	109.4	111.4	78.2
2	88.2	121.3	95.4	139.4	157.6	109.8	135.1
3	101.9	107.4	104.0	120.8	27.9	130.4	76.7
4	88.8	136.3	100.1	92.2	101.2	111.8	91.6
5	93.2	142.6	102.5	122.0	120.0	90.3	99.2
6	103.4	134.2	98.5	98.5	108.4	95.5	101.9
7	60.2	149.3	99.8	150.7	127.0	102.6	94.1
8	84.0	139.6	104.2	115.0	134.3	99.0	98.2
9	91.6	136.7	100.5	121.4	132.8	101.3	98.3
10	96.3	150.8	100.3	118.7	152.1	100.6	98.7
Mean ± SD	90.8±12.5	134.4 ±13.2	101.9±4.8	121.1±17.4	117.1±36.3	105.3±11.3	97.2±15.9

Table: The Levels of HDL- Cholesterol (mg/dl) in healthy control and diabetic groups without and with Treatments.

HDL-Cholesterol (mg/dl	Healthy control	Diabetic Groups					
		No Tx	Tx Glibin	Tx 100.0	Tx 200.0	Tx 400.0	Tx 600.0
1	49.0	24.6	17.2	52.3	55.0	63.0	36.8
2	41.3	30.1	51.5	45.0	53.6	81.0	39.3
3	38.0	27.2	34.4	39.3	67.5	54.1	37.3
4	51.0	27.3	42.9	35.8	43.1	30.4	41.8
5	39.0	28.2	38.6	39.8	59.5	47.3	38.8
6	40.6	27.6	40.8	31.1	63.0	35.8	39.3
7	45.0	28.1	39.7	20.7	24.5	49.7	39.3
8	44.0	27.8	40.2	28.3	18.8	51.6	39.8
9	49.0	27.9	40.0	36.5	23.6	50.7	39.3
10	44.0	28.0	40.1	32.4	21.2	51.1	39.6
Mean ± SD	44.1±4.5	27.7 ± 1.3	38.5±8.7	36.1±8.8	43.0±19.2	51.5±13.8	39.1±1.4

Table: The Levels of Liver P-IR (pg/mg protein) in healthy control and diabetic groups without and with treatments.

P-IR (pg/mg protein)	Healthy control	Diabetic Groups					
		No Tx	Tx Glibin	Tx 100.0	Tx 200.0	Tx 400.0	Tx 600.0
1	8.3	3.9	5.00	5.0	4.1	4.3	4.6
2	5.6	5.9	4.50	5.3	4.1	5.8	4.7
3	4.9	3.8	5.20	4.1	5.6	5.8	4.0
4	8.4	4.0	5.80	4.0	4.6	5.3	4.4
5	6.8	4.4	4.60	4.1	4.8	5.6	4.4
6	6.4	4.6	5.10	5.0	5.0	5.6	4.3
7	6.6	4.2	4.80	5.1	4.8	5.5	4.4
8	7.1	4.3	5.20	4.7	4.9	5.6	4.3
9	6.7	4.4	5.10	4.1	4.9	5.5	4.3
10	6.7	4.4	5.03	4.0	4.8	5.5	4.3
Mean ± SD	6.77±1.06	4.39±0.59	5.03±0.36	4.53± 0.53	4.77±0.43	5.45± 0.43	4.37±0.18

Table: The Levels of Liver IRS-1 (pg/mg protein) in healthy control and diabetic groups without and with treatments.

IRS-1 (pg/mg protein)	Healthy control	Diabetic Groups					
		No Tx	Tx Glibin	Tx 100.0	Tx 200.0	Tx 400.0	Tx 600.0
1	2.4	1.1	1.6	1.4	1.5	1.7	1.3
2	1.5	1.7	1.4	1.4	1.4	1.5	1.5
3	1.8	1.4	1.5	1.6	1.6	1.8	1.4
4	1.9	1.6	1.4	1.5	1.5	1.7	1.3
5	1.7	1.5	1.5	1.6	1.5	1.7	1.4
6	1.8	1.5	1.5	1.5	1.5	1.7	1.4
7	1.8	1.5	1.5	1.6	1.5	1.7	1.4
8	1.8	1.5	1.5	1.5	1.5	1.7	1.4
9	1.8	1.5	1.5	1.6	1.5	1.7	1.4
10	1.8	1.5	1.5	1.5	1.5	1.7	1.4
Mean ± SD	1.82±0.25	1.48±0.15	1.47± 0.05	1.53±0.06	1.51±0.05	1.66±0.05	1.38± 0.07

Table: The Levels of Liver PKC (pg/mg protein) in healthy control and diabetic groups without and with Treatments.

PKC (pg/mg protein)	Healthy control	Diabetic Groups					
		No Tx	Tx Glibin	Tx 100.0	Tx 200.0	Tx 400.0	Tx 600.0
1	65.9	15.1	4.3	60.3	38.0	79.9	11.1
2	29.1	37.6	72.6	60.2	34.1	54.8	41.1
3	63.2	26.3	38.5	50.0	57.8	18.4	57.3
4	52.8	32.0	55.5	56.8	43.3	39.4	51.6
5	48.4	29.2	47.0	55.7	45.1	48.1	40.3
6	54.8	30.6	51.3	54.2	48.7	40.2	47.6
7	52.0	29.9	49.1	55.5	45.7	36.5	49.2
8	51.7	30.2	50.2	54.9	46.5	41.1	47.2
9	52.8	30.0	49.7	54.9	47.0	41.5	46.0
10	52.2	30.1	49.9	55.1	46.4	39.8	47.5
Mean ± SD	52.3±9.8	29.1±5.7	46.8±17.2	55.7±3.0	45.2± 6.3	44±15.6	43.9±12.5

Table: The Levels of Muscle P-IR (pg/mg protein) in healthy control and diabetic groups without and with Treatments

P-IR (pg/mg protein)	Healthy control	Diabetic Groups					
		No Tx	Tx Glibin	Tx 100.0	Tx 200.0	Tx 400.0	Tx 600.0
1	4.3	4.8	4.3	5.5	4.3	4.2	5.2
2	7.6	3.6	4.0	4.7	5.0	4.1	4.1
3	7.1	4.0	4.1	4.1	4.7	4.8	3.9
4	5.1	3.8	4.1	4.8	4.8	4.3	4.4
5	6.0	3.9	4.1	4.8	4.7	4.4	4.1
6	6.4	3.9	4.1	4.6	4.8	4.4	4.2
7	6.2	3.9	4.1	4.7	4.8	4.5	4.2
8	5.9	3.9	4.1	4.7	4.8	4.4	4.2
9	6.0	3.9	4.1	4.7	4.8	4.4	4.2
10	6.0	3.9	4.1	4.7	4.8	4.4	4.2
Mean ± SD	6.06 ±0.92	3.95±0.33	4.12±0.08	4.72±0.33	4.74±0.17	4.38±0.18	4.27±0.35

Table: The Levels of Muscle IRS-1 (pg/mg protein) in healthy control and diabetic groups without and with Treatments.

IRS-1 (pg/mg protein)	Healthy control	Diabetic Groups					
		No Tx	Tx Glibin	Tx 100.0	Tx 200.0	Tx 400.0	Tx 600.0
1	1.3	1.6	1.4	1.5	1.6	1.4	2.0
2	1.6	1.5	1.7	1.3	1.3	1.5	1.4
3	2.0	1.6	1.6	1.6	1.5	1.5	1.0
4	1.6	1.5	1.7	1.4	1.5	1.4	1.8
5	1.7	1.6	1.6	1.4	1.4	1.5	1.5
6	1.8	1.5	1.6	1.4	1.5	1.5	1.4
7	1.7	1.5	1.6	1.4	1.5	1.5	1.4
8	1.7	1.5	1.6	1.4	1.5	1.4	1.5
9	1.7	1.5	1.6	1.4	1.5	1.5	1.5
10	1.7	1.5	1.6	1.4	1.5	1.5	1.5
Mean ± SD	1.69±0.18	1.55±0.04	1.62 ±0.08	1.44±0.06	1.46±0.09	1.46±0.03	1.5± 0.25

Table: The Levels of Muscle PKC (pg/mg protein) in healthy control and diabetic groups without and with Treatments.

PKC (pg/mg protein)	Healthy control	Diabetic Groups					
		No Tx	Tx Glibin	Tx 100.0	Tx 200.0	Tx 400.0	Tx 600.0
1	47.4	55.0	41.9	52.7	32.6	54.3	49.4
2	86.5	23.7	52.1	41.0	40.0	39.5	35.0
3	36.5	39.4	47.0	38.0	52.1	44.0	27.5
4	56.8	31.6	49.5	43.9	41.6	50.0	44.0
5	59.9	35.5	48.3	41.0	44.6	45.9	39.0
6	51.0	33.5	47.8	41.0	46.1	47.0	36.4
7	55.9	34.5	48.9	41.9	44.1	47.6	39.8
8	55.6	34.0	48.6	41.3	44.9	46.9	38.4
9	54.2	34.2	48.4	41.6	45.0	47.2	38.2
10	54.2	34.1	48.4	41.5	44.7	47.2	38.8
Mean ± SD	55.97±12.61	35.55±7.89	48.10±2.56	42.38±3.9	43.55±4.99	46.97±3.79	38.64±5.65

Table: The Levels of Muscle Glut-4 (pg/mg protein) in healthy control and diabetic groups without and with Treatments.

Glut-4 (pg/mg protein)	Healthy control	Diabetic Groups					
		No Tx	Tx Glibin	Tx 100.0	Tx 200.0	Tx 400.0	Tx 600.0
1	213.079	38.0	44.1	75.0	58.6	60.0	70.0
2	43.458	50.8	65.0	50.5	43.1	60.0	64.0
3	89.082	44.4	54.6	50.0	49.0	62.4	50.0
4	95.297	47.6	59.8	83.1	31.4	60.0	72.0
5	125.633	46.0	59.8	66.9	41.6	48.0	64.0
6	66.928	46.0	56.6	76.5	164.0	100.0	68.0
7	106.724	47.0	58.2	29.6	69.5	54.0	66.0
8	105.743	46.5	57.4	61.7	50.8	63.5	67.0
9	106.233	46.7	57.8	45.6	34.1	58.7	66.5
10	96.407	46.6	57.6	53.6	60.2	61.1	66.7
Mean ± SD	104±44.4	46.0±3.2	57.1±5.3	59.2±16.5	60.2±38.3	62.8±13.8	65.4±5.9

الملخص العربى

الداء السكري أو مرض السكري هو مجموعة من اضطرابات التمثيل الغذائي نتيجة لأسباب متعددة مما يؤدى الى ارتفاع السكر في الدم مصاحبا باضطرابات فى التمثيل الغذائى لأيض الدهون والكربوهيدرات والبروتين وذلك ناتج عن خلل في إفراز أو عمل الأنسولين، أو كليهما .وقد وجد أن آثار وأضرار مرض السكري يظهر على المدى الطويل، ويمتد أثاره إلى حدوث خلل وفشل فى وظائف أعضاء الجسم.

المرض السكرى من النوع الثانى والذى يمثل 90% من المرضى ويعد أكثر الأنواع انتشارا وأكثر تعقيداً نتيجة للتطوير التدريجى لمقاومة الأنسولين ونقص نسبى فى إفراز الأنسولين .

يشمل العلاج لمرض السكري وضع نظام غذائي، وممارسة الرياضة، واستخدام أدوية علاج السكر لخفض مستوى السكر فى الدم عن طريق الفم أو الأنسولين ويعتبر ذلك أشكال أولية من العلاج لمرض السكري .يوجد العديد من الخيارات العلاجية المتاحة حاليا وتتضمن الأدوية المخلقة أو المصنعة والتى تعتبر بجانب إنها مكلفة لها أثار جانبية خطيرة .الأدوية التكميلية أو البديلة هي مصدر مثمر للأدوية في المستقبل لمواجهة مقاومة الأنسولين .والميزة الرئيسية للطب البديل هو أنها استخدمت لعلاج الأمراض التي تصيب الإنسان لسنوات عديدة ويعتبر من الخيارات العلاجية الآمنة وغير مكلفة وتشير التقديرات إلى أن ما يصل إلى ثلث المرضى الذين يعانون من مرض السكرى تم استخدامهم لبعض أشكال الطب البديل أو التكميلى .

قرع المر هو ثمرة شعبية تستخدم لعلاج مرض السكري وهى منتشرة بين السكان الأصليين من آسيا وأمريكا الجنوبية والهند وشرق أفريقيا .وقد وثقت الدراسات الوفيرة لقرع المر فى علاج المرض السكرى ولكن الوضع الدقيق للعمل لا يزال غير واضح .كان الهدف من هذه الدراسة هو تقييم نشاط مستخلص قرع المر فى خفض مستوى السكر فى الدم والآليات الكامنة و المحتملة لعمله فى الفئران المصابة بداء مرض السكري وذلك من خلال دراسة التغيرات في مسار إشارات الأنسولين في الأنسجة الطرفية المختلفة.

لتحقيق هذا الهدف تم حث مرض السكرى كيميائيا فى ذكور الفئران البالغة من العمر 5 أيام عن طريق الحقن بالستربتوزوتوسين (١٠٠ مجم /كجم) وتم متابعة جميع الفئران التى تم حقنها لمدة تصل من ٨- ١٢ أسبوع لحدوث المرض السكري وهو ما أكده مستوى السكر الصائم في الدم أكثر من (٢٠٠ مجم / ديسيليتر). تم تقسيم الفئران المصابة بالمرض السكري إلى خمس مجموعات:

١. المجموعة الضابطة المصابة بالمرض السكري والتى لم تتلقى أي علاج.

٢. المجموعة المصابة بالمرض السكري التي تم علاجها بالمستخلص الايثانولى لقرع المر وقد تم تقسيم هذه المجموعة إلى أربع مجموعات فرعية كل مجموعة تم علاجها يوميا بجرعات مختلفة من مستخلص قرع المر (100مجم /كجم،200 ، مجم / كجم، 400 مجم / كجم،600 مجم/كجم) وذلك لمدة 30 يوما .

٣. المجموعة التي عولجت بجليبنكلاميد 0.1 مجم / كجم لمدة 30 يوما .

٤. المجموعة الضابطة (الفئران الأصحاء).

وبعد 30 يوم من العلاج تم جمع الدم وتشريح جميع المجموعات للحصول على أنسجة الكبد والعضلات لتعيين دلالات إشارات الأنسولين.

وقد أشارت النتائج إلى أن الفئران التى تم حقنها بالستربتوزوتوسين قد أظهرت مظاهر نموذجية للمرض السكري من النوع الثانى .بما في ذلك زيادة فى الوزن، ارتفاع مستوى السكر في الدم، وانخفاض مستوى الأنسولين وارتفاع مؤشر مقاومة الأنسولين (HOMA) وأيضا هذا الخلل فى توازن الجلوكوز مرتبط بحدوث خلل فى أيض الدهون حيث ظهرت فى زيادة الدهون الثلاثية والكولسترول الكلي والكولسترول الضار، وانخفاض في الكولسترول النافع.

وقد أظهرت نتائج العلاج بالمستخلص الايثانولى لقرع المر معتمدا على جرعة العلاج حدوث انخفاض في وزن الجسم وزيادة في مستوى الأنسولين بينما أظهرت نسبة السكر الصائم في الدم ومؤشر مقاومة الأنسولين انخفاض فى المستوى وذلك فى الجرعات (١٠٠- ٤٠٠ مجم/كجم) وقد وجد أن جرعة العلاج 400 مجم /كجم هى أفضل النتائج ، و عندما تم مقارنة فاعلية قرع المر مع الأدوية المخلقة مثل السلفونيل يوريا (جليبنكلاميد) وجد أن مستخلص قرع المر فى جرعة 400 مجم/كجم أظهرت تحسينات مماثلة للجليبنكلاميد في دلالات توازن الجلوكوز.

وقد ارتبط مقاومة الأنسولين في الفئران المصابة بالمرض السكري بخلل فى مسار إشارات الأنسولين في الكبد والعضلات والذى ظهر من خلال انخفاض مستقبلات الأنسولين (Glut-4, PKC, IRS-1, P-IR) وقد أظهر العلاج بقرع المر زيادة فى العديد من مكونات مسار إشارات الأنسولين في الكبد والعضلات معتمداً على الجرعة وذلك من ١٠٠- ٤٠٠ مجم / كجم في حين أظهرت أعلى جرعة (600مجم/كجم) تأثير أقل كفاءة من جرعات أقل .هذا التأثير المحث على التعبير عن هذه المكونات من إشارات الأنسولين على المستوى البروتينى لهم ويشير إلى أن مكونات قرع المر قد يكون بمثابة منظم إيجابي في التعبير الجيني.،

وقد تبين أيضا أن العلاج بقرع المر له تأثيره فى خفض الدهون الثلاثية في الجرعات المنخفضة (100 و 200 مجم / كجم) في حين أن الجرعات العالية ليس لها تأثير كبير.بينما أظهر الكوليسترول تصحيح معتدل مع العلاج بقرع المر . في حين أظهر العلاج بمستخلص قرع المر زيادة الكولسترول النافع-و انخفاض الكولسترول الضار معتمدا على الجرعة بجرعات ١٠٠- ٤٠٠ مجم / كجم في حين أظهرت أعلى جرعة تأثير أقل كما أظهر أيضا جليبينكلاميد تصحيح جزئي لدلالات الدهون .

من نتائج هذه الدراسة وغيرها من الدراسات ذات الصلة يمكن أن نستنتج ما يلي:

١- مستخلص قرع المر هو عامل قوى لتخفيض مستوى السكر والذى يلعب دورا هاما لعلاج المرض السكري.

٢- قرع المر له تأثيره من خلال مسارات متعددة:

أ - له تأثير مثل تأثير إفراز الأنسولين، مما يحفز على إفراز الأنسولين من خلايا بيتا .

ب- يحاكى عمل الانسولين، من خلال مكوناته مثل الأنسولين بى (بولى ببتيد بى) (p-insulin / polypeptide P) مما يحفز على عمل مماثل للانسولين في الأنسجة الطرفية.

ج- يحث الأنسجة الطرفية علي التعبير أو إظهار إشارات الأنسولين مما يعمل بمثابة الأنسولين المحفز أو المحسس.

٣- مستخلص نبات قرع المر في الجرعات المنخفضة يظهر تأثير مماثل للجليبنكلاميد (السلفونيل يوريا) بينما الجرعة العالية هى أقل كفاءة وربما يؤدي إلى تفاقم المرض السكري .

٤- مستخلص قرع المر يكون له تأثير فى خفض الدهون مما يصحح جزئيا مرض (dyslipidemia) في الفئران المصابة بالمرض السكري.

٥- ينصح بقرع المر كمكمل غذائي لعلاج النوع الثانى من مرض السكري

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كلية العلوم

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مقدمة من

هالة محمد عبد البارى حسن الحاج

للحصول على درجة

الدكتوراه

في

الكيمياء الحيوية

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رسالة مقدمة إلي
معهد البحوث الطبية - جامعة الإسكندرية
إيفاء جزئيا للحصول على درجة

الدكتوراه في الكيمياء الحيوية

من

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