CHAPTER 2

LITERATURE REVIEW

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2.1 Diabetes Mellitus

Diabetes Mellitus is a group of chronic metabolic disorders characterized by chronic hyperglycaemia as a result of relative or absolute lack of insulin or the actions of insulin (Kumar and Clark, 2002). Chronic hyperglycaemia during diabetes increase non enzymatic glycation of proteins that later leads to secondary complication. These complications include hypoglycaemia, diabetic ketoacidosis, non-ketotic syndrome, thirst, polyuria, visual blurriness, weight loss, hypertension, neuropathy, nephropathy and retinopathy. Several hypoglycaemic drugs, insulin injections and life style changes, such as exercise, weight control and diets have been employed for the treatment of diabetes (Knentz and Nattras, 1991; Kumar and Clark, 2002). However, the management of this disease is still a challenge to the medical system (Kameswararao et al., 2003). This is because none of these hypoglycaemic drugs were able to cure diabetes without causing any adverse side effects. These effects have led to an increase in the prevalence of DM worldwide. Recently, much attention has been focused on antidiabetic plants used in traditional medicine mostly because of better treatment than the modern western medicine.

2.1.1 Types of diabetes mellitus

There are three main types of diabetes mellitus namely: type 1 diabetes (insulin-dependent diabetes mellitus), type 2 diabetes (non insulin- dependent diabetes mellitus) and

gestational diabetes. The symptoms of these forms of diabetes are similar but vary in their intensity. Type 1 DM is caused by immunological destruction of pancreatic β cells leading to absolute insulin deficiency (Notkins, 2002). It is a juvenile disease with 10 % prevalence among diabetic patients worldwide (Ranjan et al., 2002). Patients affected by this form of diabetes are completely dependent on exogenous insulin to maintain a normal life style. Type 2 is another form of DM characterized with insulin resistance and is the most common type of diabetes afflicting 85-95 % of all diabetic individuals over 40 years of age (Lanza et al., 1999). Gestational diabetes is a common disorder that occurs mostly during pregnancy due to hormonal changes or insulin deficiency. It affects approximately 7 % of pregnancies each year (ADA, 2000). This disorder can increase the risk of developing type 2 DM for both mother and the baby if not properly managed.

2.1.2 Cause and prevalence of diabetes mellitus

The causes of diabetes are not clearly known. However it is associated with risk factors that are considered to be the pathogenesis of this disease. These factors include consumption of calorie- rich diet, hereditary, obesity, sedentary life style, smoking, virus infection, age, socio-economic status as well as increasing number of ageing population. The number of people suffering from the disease worldwide is increasing at an alarming rate. According to Wild et al. (2004) about 366 million people were projected to be diabetic by the year 2030 against 191 million estimated in 2000. All over the world, India is ranked as the country with the highest diabetic patients followed by China and United State of America. Unfortunately, Africa and Asia were recently identified as regions where the number of diabetics could rise above the predicted level (ADA, 2006). In South Africa, the prevalence of people suffering from diabetes has been rising steadily over the past two decades. The

prevalence is predicted to hit 3.9 % of the South African population between the age of 20 and 79 by the year 2025 (www.eatlas.idf.org). Insufficient promising therapy to cure diabetes could be responsible for the predicted figure in this part of the world.

2.2 Insulin

Insulin is a peptide hormone secreted by pancreatic β-cells in response to increased blood glucose levels. It was first discovered by Canadian scientists in the year 1921 due to increase death rate of people suffering from type 1 diabetes (Bliss, 1982). Insulin has a molecular weight of 6,000 Daltons with two subunits held together by disulphide bonds. It is secreted in significant amounts as preproinsulin in the ribosome of endoplasmic reticulum. The cleavage of signal peptide of preproinsulin results in the formation of proinsulin and later matures into insulin through the action of endo-peptidases (ADA, 1997).

2.2.1 Mechanism of insulin biosynthesis

The secretion of insulin from pancreatic β cells is a complex process involving a glucose induced biphasic pattern of insulin release. Defects in both phases of insulin secretion may be the earliest detectable stage of type 2 diabetes (Gerich, 2002). Secretion of insulin is based on K_{ATP} channels which are grouped into two principal signaling pathways. These are ATP - dependent and ATP ‗ independent K^+ channels (Chow et al., 1995; Straub and Sharp, 2002). In the K_{ATP} channel pathway, ATP derived from the glycolytic metabolism of glucose closes the K_{ATP} channels and causes β- cell membrane depolarization. The resulting opening of voltage-dependent L-type Ca^{2+} channels increases influx of extracellular Ca^{2+} into the β- cells, leading to rise in $[Ca^{2+}]_i$ which triggers the

release of insulin (Yang and Gillis, 2004). On the other hand, the mechanisms involved in the ATP -independent channel are yet to be defined. Nevertheless, several signaling pathways are employed in this channel for the secretion of insulin. These include mitochondria-generated signaling, Adenylate cyclase and PKA signaling, PLA_2 and arachidonic acid signaling pathways (Chow et al., 1995).

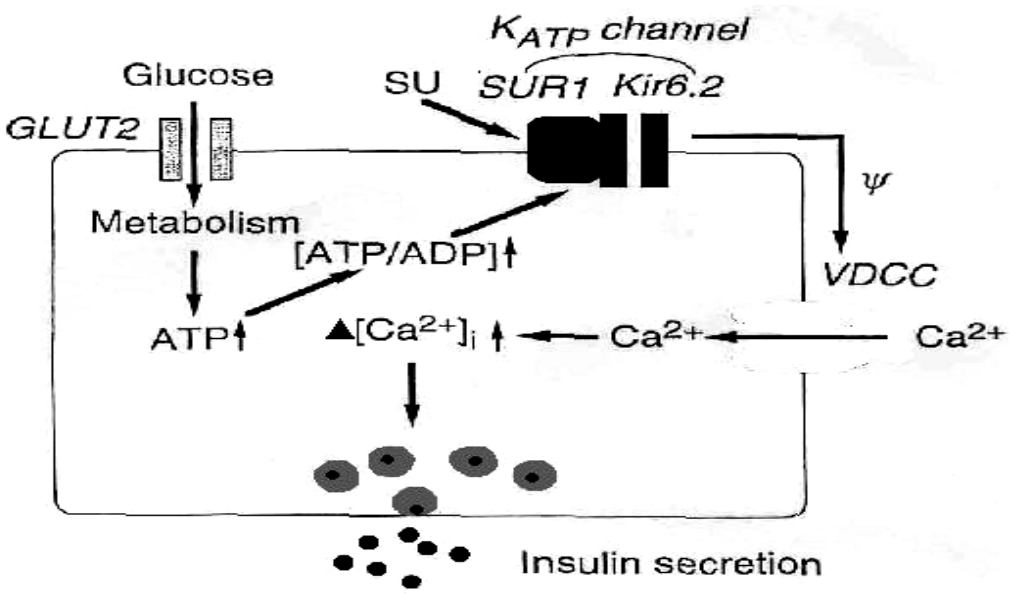

Figure 2: The major pathway of glucose induced and sulfonylurea (SU) -induced insulin secretion. GLUT 2 (glucose transporter 2); VDCC- voltage-dependent calcium channel.

2.3 Functions of insulin

Insulin is a potent anabolic hormone that stimulates the uptake and storage of glucose, fatty acids and amino acids into glycogen, fat and protein respectively. It regulates glucose homeostasis, storage of glycogen and formation of triglycerides, in different target tissues as shown in Figure 2. It is also known to modulate transcriptional processes, replication of cells, DNA synthesis and increase amino acid transport into cells as well as to stimulate lipogenesis (Nakae and Accili, 1999).

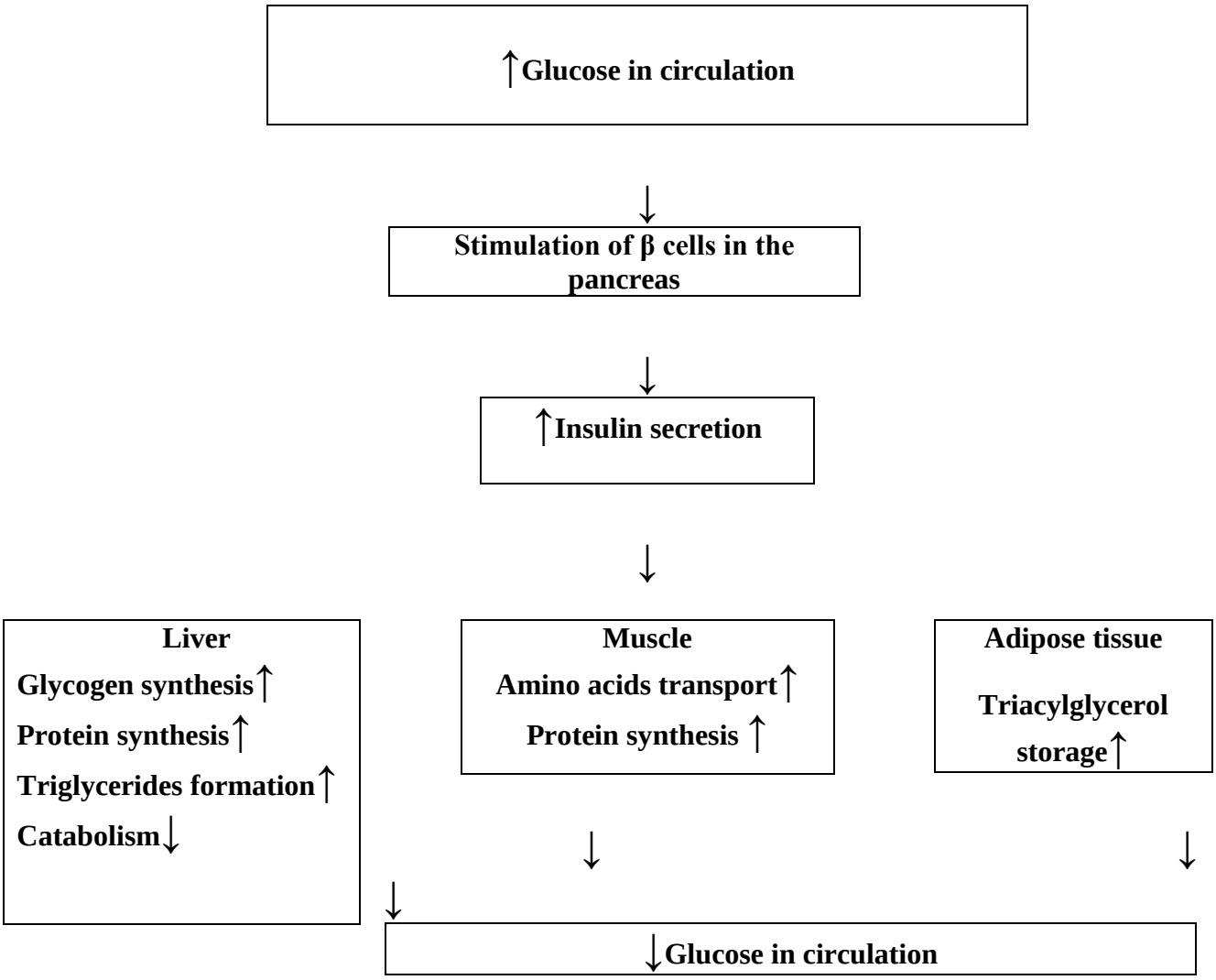

Figure 3: Schematic diagram of function of insulin

2.3.1 Glucose metabolism

Glucose is the prime fuel for the generation of energy with the formula $C_6H_{12}O_6$. During fasting, glucagon is secreted which break down liver glycogen and thus leads to the synthesis of glucose through gluconeogenesis pathway after depletion of glycogen (Voet et al., 2002). Activation of glucagon raises the glucose level in the blood by binding to the tissue receptors to activate adenylyl cyclase which is linked to the cAMP (cyclic adenosine monophosphate) mediated cascade (Figure 3).

2.3.2 Glucose transport

The action of insulin in glucose uptake, involves translocation of glucose transporter proteins (GLUTs) from intracellular compartments to the cellular membrane where glucose uptake is being facilitated (Cushman and Wardzala, 1980). Transport of glucose is initiated upon binding of insulin to the insulin receptor (Schaffer et al., 2003). This binding results into a conformational change and auto-phosphorylations of the receptors as shown in Figure 4. Among several insulin receptors substrates (IRS), IRS1 is recruited and binds to a phosphotyrosine residue (Chen et al., 1996). The increase in enzyme activity of phosphoinositide-3-kinase enhances the recruitment of Protien Kinase B to bind with the plasma membrane (Eldar et al., 1997; Lodish et al., 2004). After localizing on the membrane, protein kinase B is phosphorylated by two membrane bound kinases and then released into the cytosol where glucose uptake and glycogen synthesis are stimulated (Foulds et al., 2004; Lodish et al., 2004). It has been reported that glucose homeostasis is regulated by insulin via uptake of glucose into skeletal muscle, and to a lesser extent, into the liver and adipose tissue (Fielding and Frayn, 1998).

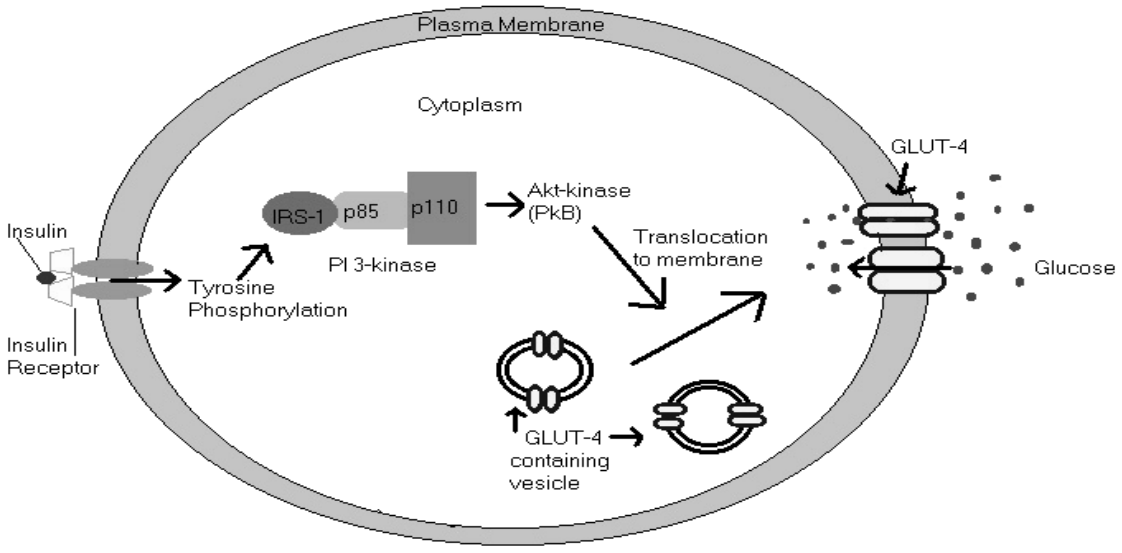

Figure 4: Insulin Signaling Pathway for Glucose Transport Chain (Chen et al., 1996).

2.3.3 Insulin facilitates glucose uptake in the target tissues

Skeletal muscle is one of the key tissues involved in the maintenance of whole body glucose homeostasis. It takes up glucose from the circulation in response to insulin, and is largely responsible for clearing post-prandial hyperglycemia (Moore et al., 2003). The increased glucose uptake by skeletal muscle is mediated by type 4 glucose transporter (GLUT4), which is stored in intracellular vesicles in the absence of insulin (Mueckler, 1994). The adipose tissue is another major site for the uptake of dietary fatty acids. It releases energy in the form of fatty acids (Fielding and Frayn, 1998). In the presence of insulin (Figure 4), adipocytes take up glucose and lipids from the blood and store them as triacylglycerol. After the meal, the adipose tissue functions to supply energy for other tissues by releasing free fatty acid (FFAs) into circulation in the form of chylomicrons for energy production (Fielding and Frayn, 1998). Hepatocytes take up glucose through glucose transporter 2 (GLUT 2) localised at the plasma membrane (Bary and Horuk, 1984). When glucose enters the hepatocytes through facilitated diffusion mechanism, it is retained through conversion by hepatic glucokinase to glucose-6-phosphate in the glycolytic pathways (Pilkis and Granner, 1992; Zhang et al., 2002).

2.3.4 Lipids metabolism

In humans, another major source of fuel or energy apart from carbohydrate is lipids. Lipids are water insoluble biomolecules which includes phospholipids, triglycerides, glycolipids and sterols. Triglycerides among other lipids represent the storage form mainly in the adipocytes and are composed of glycerol and three fatty acid molecules. It is hydrolyzed into free fatty acids and mono-acylglycerols by a process called lipolysis. This process involves multiple lipases that are produced by gastric mucosa and pancreatic cells (Park and Hellerstein, 2000). Free fatty acids and mono-acylglycerols are re-esterified into triglycerides

after uptake by intestinal cells into chylomicrons. Chylomicrons are particles containing a hydrophobic core of triglycerides and cholesteryl esters surrounded by a monolayer of phospholipids and cholesterol. The lipids in these particles both triglycerides and cholesterol are taken up by hepatic and peripheral tissues, mainly muscle and adipose tissue by the action of lipases. In addition, triglycerides are also uptake by the liver from very- low density lipoprotein (VLDL) by which the secretion is regulated by insulin (Park et al., 1999).

2.4 Western medicine for diabetes treatment

Several hypoglycaemic drugs have been employed for the treatment of diabetes with different mechanism of actions. These include sulphonylureas, metformin, acarbose, thiazolidinedione, glibenclamide and insulin. Metformin is a first-line drug of choice for the treatment of type 2 diabetes especially in overweight and obese people (ADA, 2000). It increases insulin sensitivity by suppressing hepatic glucose production as well as increasing muscle glucose uptake. The molecular targets of this drug are currently unknown but activation of the adenosine mono-phosphate (AMP) activated protein kinase has been reported to play an important role (Bailey and Dominiczak, 2004). Sulphonylureas are another first line treatment of type 2 diabetes that acts directly on the pancreatic β cells to potentiate insulin secretion. Acarbose is a new therapeutic drug used basically to inhibit α - glucosidase without directly interfering with glucose uptake (Wehmeier and Piepersberg, 2004). It is often used in combinational therapy with other drugs or insulin to lower the blood glucose level. Rosiglitazone and pioglitazone are thiazolidinedione currently used to improve the body's response to insulin by lowering insulin resistance in the cells. The molecular target for thiazolidinedione is the peroxisome proliferator-activated receptor γ (PPAR), where it acts as an agonist (Suzuki et al., 2010). Lastly, insulin treatment is used in a later stage of type 2

DM progression, when pancreatic β cells can no longer secrete a sufficient amount of insulin to maintain an acceptable glucose concentration in the circulation. It is a life dependent drug for type 1 diabetic patients.

2.5 Limitation to western medicine

The limitation encountered from the use of modern antidiabetic drugs could be linked to the undirectional therapeutic approach, high cost and the presence of adverse side effects (Tiwari and Rao, 2002). For example, the use of sulphonylureas has been reported to worsen heart disease, increase body weight and induce hypoglycaemia (Dey et al., 2003). Liver toxicity was observed in patients treated with thiazolidinedione while diarrhea, abdominal discomfort, flatulence and pain were shown in patients taking glucosidase inhibitors (De Fronzo, 1999). Hypoglycaemia and other symptoms including nausea, hunger, tiredness, palpitation and headache have also been reported as major side effects of insulin therapy (www.medicinenet.com/insulin). Another important factor of western medicine limitation could be attributed to the belief that herbs do provide some benefits over and above allopathic medicine and allow the users to feel that they have some control in their choice of medication (Joshi and Kaul, 2001). These drugs are very expensive and as a result beyond the reach of diabetic patients especially those living in the rural areas. Therefore, there is need to search for natural products of plant origin as a source of novel molecules that can complement the drugs currently used to negate the adverse side effects of western medicine (Marles and Farnsworth, 1995).

2.6 Alternative medicine

Insulin was first introduced in 1922 for the treatment of diabetes, before then diabetes treatment relied heavily on dietary measures which included the use of medicinal plant therapies. Medicinal plants have been used in traditional medicines, since time immemorial to maintain health or cure ailments from the dawn of civilization (Kalemba and Kunicka, 2003). It has been a rich source of new drug discovery. For example, metformin the most commonly used antidiabetic drug was discovered from *Galega officinalis* since the Middle Ages because of its richness in guanidine (Bailey and Day, 2004). In the last few years there has been an exponential growth in the field of herbal medicine and these plants are gaining popularity in some countries for primary health care because of their wide biological and medicinal activities, lower side effects and lesser costs (Farnsworth, 1994). Herbal medicines continue to play an important role in diabetic therapy, particularly in the developing countries where most people have limited resources and do not have access to modern treatment (Ali et al., 2006). The use of herbal medicine for the treatment of diabetes has been authenticated (WHO, 1980) due to the presence of phytochemicals with antidiabetic properties. Some of these compounds include fibres, vitamins, minerals, secondary metabolites and xanthones (Day, 1998). The increase in demand for the use of plant based medicines to treat diabetes may be due to the side effects associated with the use of orthodox drugs such as insulin and oral hypoglycemic agents (Marles and Farnsworth, 1995). Another important factor that strengthens the use of plant materials as antidiabetic could be attributed to the belief that herbs do provide some benefits over and above allopathic medicine and allow the users to feel that they have some control in their choice of medication (Joshi and Kaul, 2001). However, few of these plants have received scientific or medical scrutiny as recommended by the World Health Organization.

2.6.1 Mechanisms of actions of antidiabetic plants

Several antidiabetic plants have been reported in different parts of the world for the treatment of diabetes with different therapeutic targets (Edwin et al., 2008). Some were investigated in streptozotocin (STZ) and alloxan induced diabetic rats at different dosages to evaluate their antidiabetic potentials. Majority of these plants displayed antihyperglycaemic properties while few have shown hypoglycaemic effect. Some of the mechanisms of action reported are related to inhibition of mitochondrial function, stimulation of glycolysis, activation of AMPK (adenosine mono-phosphate kinase) pathway, suppression of adipogenesis, uptake of glucose and induction of low density lipoprotein (Jun et al., 2009; Matsui et al., 2006). In addition, some plants with antidiabetic properties have also been reported to inhibit carbohydrate digestive enzymes such as α- glucosidase and α- amylase (Shibib et al., 1993). Antioxidant properties and modification of insulin structure or insulin receptor sensitivity as well as up-regulation of glucose transporter of some plants have been reported in several studies (Day, 1990; Cummings et al., 2002; Hardman and Limberd, 2001). Although, the metabolic activities of these plants are well established, the molecular mechanism underlying their biological activities remains unknown. Many South African medicinal plants have been investigated which include *Leonotis leonurus*, *Sutherlandia frutescens*, *Cissampelo capensis*, *Schotia latifolia*, *Vernonia amygdalina* and *Momordica foetis.* These plants among others have been reported to possess anti-hyperglycemia, hypoglycaemic, hypolipidaemic and anti-obesity properties due to their action on insulin sensitization, β- cell preservation and antioxidant activities (Jeevathayaparan et al., 1995). Many other antidiabetic plants have been reported as scavenger of free radicals generated at the onset and during diabetic state in the experimental animals (Rice-Evans et al., 1996).

REFERENCES

Ali, H., Houghton, P.J and Soumyanath, A (2006). A-amylase inhibitory activity of some Malaysian plants used to treat diabetes: with reference to Phyllanthus amarus. J. Ethnopharmacol. 107:449-455.

American Diabetes Association (2000). Gestational diabetes mellitus. Diabetes Care. 23: S77-S79.

American Diabetes Association (2002). Implications of the United Kingdom Prospectives Diabetes study (Position Statement). Diabetes Care 25 (Suppl.1):S28-S32.

American diabetes Association (2006). Third party reimbursement for diabetes care, self management education and supplies. Diabetes care. 29 (Suppl.1): S68-S69.

American Diabetes Association (2007). Standards of medical care for patients with diabetes mellitus. Diabetes Care. 20: 518–520.

Bailey, C.J and Day, C (2004). Avandment: Combined metformin-rosiglitazone treatment for insulin resistance in type 2 diabetes. Int J Clin Pract. 58: 867-876.

Bailey, C.J., Flatt, P.R and Marks, V (1989). Drugs inducing hypoglycaemia. Pharmacol, Therapeutics. 42:361-384.

Bary, D.L and Horuk, R (1984). Dissociation of insulin-stimulated glucose transport from the translocation of glucose carriers in rat adipose cells. J Biol Chem. 262 (1): 21-24.

Baynes, J and Dominiczak, M (2004) Glucose homeostasis and fuel metabolism. Med Biochem. 2nd edn. 243-266.

Bliss, M (1921). The discovery of insulin, 2nd edn. Toronto: University of Toronto Press.

Chen, J., Sadowski H.B., Kohanski, R.A and Wang, L (1996). Stat5 is a physiological substrate of the insulin receptor. Proceedings of the National Academy of Science. 94: 2295-2300.

Chow, K.H., Kiefl, R.F., MacFarlane, W.A., Schneider, J.W., Cooke, D.W., Leon, M., Paciotti, M., Estle, TL., Hitti, B., Lichti, RL., Cox, SF., Schwab, C., Davis, EA., Morrobel-Sosa, A and Zayieh, L (1995). Structure of negatively charged muonium in n-type GaAs. Phys. Rev. B52: 16939-16942.

Cummings, E., Hundal, H., Wackerhage, H., Woods, N and Singh, J (2002). Effect of *Mormodica charantia* fruit juice on glucose and amino acid transport in L6 myotubes. J Physiol. 5: (4): 3-14.

Cushman, SW and Wardzala, L.J (1980). Potential mechanism of insulin action on glucose transport in the isolated rat adipose cell. Apparent translocation of intracellular transport systems to the plasma membrane. J. Biol. Chem. 255 (10): 4758-4762.

Day, C (1998). Traditional plants treatments of diabetes mellitus: Pharmaceutical foods. Brit. J. Nutr. 80:5-6.

Day, C., Cartwright, T., Provost, J and Bailey, C.J (1990). Hypoglycaemic effect of *Mormodica charantia* extracts. Planta Med. 56: 426-429.

De Fronzo, RA (1999). Pharmacology theraphy for type 2 diabetes mellitus. *Ann.* Intern. Med. 131: 281-303.

Dey, L., Xie, J.T., Wang, A., Wu, J., Maleckar, S.A and Yuan, C.S (2003). Anti-hyperglycemic effects of ginseng: comparison root and berry. Phytomedicine 10: 600-605.

Edwin, E., Sheeja, E., Gupta, V.B and Jain, D.C (2008). Fight Diabetes the herbal way review. Express Pharma. 1: 41-42.

Eldar-Finkelman, H and Krebs, E.G (1997). Phosphorylation of insulin receptor substrate 1 by glycogen synthase kinase 3 impairs insulin action. Proceedings of the National Academy of Science. 94: 9660-9664.

Elvin-Lewis, M (2001). Should we be concerned about herbal remedies? J. Ethnopharmacol. 75: 141-164.

Farnsworth, N.R (1994). Ethnopharmacology and drug development. Ciba found Symp. 185: 42-59.

Fielding, B.A and Frayn, K.N (1998). Lipoprotein lipase and the disposition of dietary fatty acids. Brit. J. Nutr. 80(6): 495-502.

Foulds, C.E., Nelson, M.L., Blaszczak, A.G and Graves, B.J (2004). Ras/Mitogen-Activated Protein Kinase Signaling Activates Ets-1 and Ets-2 by CBP/p300 Recruitment. Mol and Cell Biol. 24(24): 10954-10964.

Gerich, J.E (2002). Is reduced first-phase insulin release the earliest detecteble abnormality in individuals destined to develop type 2 diabetes? Diabetes. 51(1): S117-S121.

Hardman, J.G and Limberd, L.E (2001). Insulin, oral hypoglycemic agents and The Pharmacology of the endocrine pancreas. In Goodman and Gilman's: The Pharmacological basis of Therapeutics. Tenth edition. Mcgraw-Hill Company Limited, USA.

Jeevathayaparan, S., Tennekoon, K.H and Karunanayake, E.H (1995). A comparative study of the oral hypoglyceamic effect of *Mormodica charantia* fruit juice and tobultamide in streptozotocin induced graded severity diabetes in the rat. Int J Diabetes. 3: 99-108.

Joshi, B.J and Kaul, P.N (2001). Alternative medicine: herbal drugs and their critical appraisal. Prog Drug Res. 56:1-76.

Jun, Y., Hanjie, Z and Jianping, Y (2008). Traditional Chinese Medicine in Treatment of Metabolic Syndrome. Endocr Metab Immune Disord Drug Targets. 8(2): 99-111.

Kalemba, D and Kunicka, A (2003). Antibacterial and antifungal properties of essential oils. Curr Med Chem.10: 813-829.

Kameswararao, B., Kesavulu, M.M and Apparao, C (2003). Evaluation of antidiabetic effect of Monordica cymbalaria fruit in alloxan-diabetic rats. Fitote*r*. 74: 7-13.

Knentz, A.J and Nattras, M (1991). Diabetic ketoacidosis, non ketotic hyperosmolar coma and lactic acidosis. In: handbook of diabetes Pickup, JC and Williams, G (2nd editions). Blackwell Sci.

Kumar, P and Clark, M (2002). Diabetes mellitus and other disorders of metabolism. In: Clinical Medicine. WB Sunders, London.

Lanza, R.P., Ecker, D.M., Kuhtreiber, W.M., Marsh, J.P., Ringelling, J and Chink, W.L (1999). Transplantation of islets using micro encapsulation: studies in diabetic rodents and dogs. J. Mol Med. 77: 206-210.

Lodish, H., Berk, A., Matsudaira, P., Kaiser, C.A., Krieger, M., Scott, M.P., Zipursky, L and Darnell, J (2004). Molecular Cell Biology, Fifth Edition. Freeman books.

Marles, R.J and Farnsworth, N.R (1995). Antidiabetic plants and their active constituents. Phytomedicine. 2: 137-189.

Matsuri, Y., Shimura, S., Suto, Y et al. (2006). A novel femoral arterial cannula to prevent limb ishaemia during cardiopulmonary support: preliminary report of experimental and clinical experiences. Artif Org. 30:557-560.

Mueckler, M (1994). Facilitative glucose transporters. Eur J. Biochem. 219: 713-725.

Nakae, J and Accili, D. (1999). The mechanism of insulin action. J. Pediatr. Endocrinol. Metab 12: 721-731.

Notkins, A.L (2002). Immunologic and genetic factors in type 1 diabetes. J. Biol. Chem. 277: 43545-43548.

Parks, E.J., Krauss, RM., Neese, RA., Hellerstein, MK. (1999). Effects of a low-fat, high-carbohydrate diet on VLDL-triglyceride assembly, production and clearance. J. Clin. Invest. 104: 1087-1096.

Parks, E and Hellerstein, M.K (2000). Carbohydrate-induced hypertriglycerolemia: an historical perspective and review of biological mechanisms. Am. J. Clin. Nutr 71: 412-433.

Pilkis, S.J and Granner, D.K (1992). Molecular physiology of the regulation of hepatic gluconeogenesis and glycolysis. Ann Rev Physiol. 54: 885-909.

Ranjan, C and Ramanujam, R (2002). Diabetes and insulin resistance associated disorders: Disease and the therapy. Curr Sci. 83:1533-1538.

Rice-Evans, C.A., Miller, N.J., Bolwell, P.G., Bramley, P.M and Pridham, J.B (1995). The relative activities of plant-derived polyphenolic flavonoids. Free radical Res. 22:375-383.

Scaffer, L., Brissette, RE., Spetzler, JC., Pillutla, RC., Østergaard, S., Lennick, M., Brandt, J., Fletcher, PW., Danielsen, GM., Hsiao, K., Andersen, AS., Dedova, O., Ribel, U., Hoeg-Jensen, T., Hansen, P., Blume, AJ., Markussen, J and Goldstein, NL (2003). Assembly of high affinity insulin receptor agonists and antagonists from peptide building blocks. Proc Natl Acad of Sci. 100(8): 4435-4439.

Shibib, B.A., Khan, L.A and Rahman, R (1993). Hypoglycemic activity of *Coccinia indica* and *Mormodica charantia* in diabetic rats: Depression of the hepatic gluconeogenic enzymes glucose 6 phosphates and fructose 1,6 biphosphatase and elevation of both liver and red cell shunt enzyme glucose 6 phosphatase dehydrogenase. Biochem. J. 292:267-270.

Straub, S.G and Sharp, G.W (2002). Glucose-stimulated signaling pathways in biphasic insulin secretion. Diabetes Metab Res Rev. 18(6): 451-463.

Sumana, G and Suryawanshi, S.A (2001). Effect of vinca rosea extracts in treatment of alloxan diabetes in male albino rats. Indian J Exp Biol. 39: 748-758.

Suzuki, S., Arnold, L.L., Pennington, K.L., Kakiuchi-Kiyota, S., Wei, M., Wanibuchi, H and Cohen, S.M (2010). Effects of pioglitazone, a Peroxisome Proliferator-Activated Receptor Gamma Agonist, on the Urine and Urothelium of the rat. Toxicol Sci. 113:349-357.

Tiwari, A.K and Rao, J.M (2002). Diabetic mellitus and multiple therapeutic approaches of phytochemicals: Present status and future prospects. Curr. Sci. 83: 30-37.

Voet, D., Voet J.G and Pratt, C.W (2002). Fundamentals of Biochemistry. John Wiley and Sons, Inc. New York, NY.

Wehmeier, U.F and Piepersberg, W (2004). Biotechnology and molecular biology of the alpha glucosidase inhibitor Acarbose. Microbiol. Biotechnol. 63:613-625.

WHO. Expert committee on diabetes mellitus (1980). Second Report Technical. Report. Series 646. World Health Organisation Geneva.

Wild, SG., Roglic, A., Green, R and King, H (2004). Global prevalence of diabetes. Estimated for the year 2000 and projection for 2030. Diabetes care 27:1047-1054.

Yang, Y and Gillis, K.D (2004). A highly Ca^{2+} sensitive pool of granules is regulated by glucose and protein kinases in insulin secreting INS-1 cells. J. Gen. Physiol. 124:641-651.

Zhang, X., Gan, L., Pan, H., Guo, S., He, X., Olson, S.T., Mesecar, A., Adam, S and Unterman, T.G (2002). Phosphorylation of serine 256 suppresses transactivation by FKHR (FOXO1) by multiple mechanisms. Direct and indirect effects on nuclear/cytoplasm shuttling and DNA binding. J. Biol Chem. 277: 45276-45284.