2.0 Review of Literature

Type 1 Diabetes is of two categories, Type 1A and Type 1B. Immune-mediated diabetes (Type 1A) results from a cellular-mediated autoimmune destruction of the beta cells of the pancreas. Markers of the immune destruction of the beta cell include islet cell autoantibodies and other antibodies with strong HLA associations.

Idiopathic diabetes (Type 1B) appears to result from known etiologies. A few patients have permanent insulin deficiency and are prone to ketoacidosis but have no evidence of autoimmunity. Individuals with this form of diabetes suffer from episodic ketoacidosis and exhibit varying degrees of insulin deficiency between episodes. This form of diabetes is strongly inherited, lacks immunological evidence for beta cell autoimmunity, and is not HLA associated. An absolute requirement for insulin replacement therapy in affected patients may vary.

Acute or chronic inflammation is thought to play a major role in the etiology and/or pathogenesis of autoimmune disease. Thus, by blocking the initial inflammatory insult one could in theory prevent the excessive attraction of autoaggressive lymphocytes to the inflammation site and the subsequent formation of a pattern that leads to autoimmune disease (Christen, 2007). Correlation studies between cytokines expressed in islets and autoimmune diabetes development in animal models suggest β-cell destruction is associated with increased TH 1 and pro-inflammatory cytokines. The pro-inflammatory cytokines involved were interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α) and interferon-γ (IFN-γ) (Major, 2000) Although necrosis also plays a role, β-cell death by apoptosis precipitates T1D and also contributes to both T2D and islet graft failure after transplantation (Cnopet et al., 2005).
There are two gene families that are particularly important in the control of apoptosis: the genes encoding the interleukin-1–converting enzyme (ICE) family of cysteine proteases (now known as caspases), and those related to the protooncogene bcl-2 (Mauricio and Mandrup-Poulsen, 1998). Bax activation underlies cytochrome C release and caspase-9 cleavage and places the BH3-only protein Bad as an upstream regulator. The BH3-only protein Bad and the downstream multidomain effector molecules Bax and Bak are required for cytokine-induced β-cell death (McKenzie et al., 2008). There is an independent evidence for the role of a phosphorylation-dependent interplay of Bad with glucokinase in the maintenance of glucose-stimulated insulin secretion (Danialet al., 2008). Thus, in addition to its potential role in cytokine-mediated death Bad might also contribute to secretory defects in the context of T1D as well as T2D (Thomas and Biden, 2009). Also a c-Jun NH2-terminal kinase (JNK) is a key player in β-cell apoptosis in models of T1D (Bonny et al., 2001).

The over expression of the prosurvival molecule Bcl-2 partially protects β-cells from cytokine toxicity (Rabinovitch et al., 1999).

Signal transduction by these cytokines involves binding to specific receptors, and that of cytosolic kinases (especially the so-called mitogen- and stress-activated protein kinases) and/or phosphatases, mobilization of diverse transcription and nuclear factor kappaB (NF-kappaB), AP-1 and STAT-1 probably playing key roles for beta-cell apoptosis and up-regulation and down-regulation of gene transcription. (Eizirik and Mandrup-Poulsen 2001).

First evidence that human cytomegalovirus may be involved in the loss of tolerance to autoantigen GAD65 was demonstrated wherein, T cells reactive to GAD65 cross-reacted with a peptide of the human cytomegalovirus major DNA binding protein (Roep et al., 2002).
The non-obese diabetic (NOD) mouse is widely considered the existing suitable animal model of Type I Diabetes in which the autoimmune destruction of the islet β cells closely resembles the pattern seen in human (Kolb, 1987). Bio Bred rats also have a genetic predisposition to develop diabetes at about 20 to 60 days of age. LCMEV (Leucocytic Meningio Encephalytis Virus) infected mice have also reported to produce certain autoantigens of Type 1 Diabetes. Other chemically induced NIDDM models use Dithiazone, alloxan, streptozocin or Dexamethasone. The destruction of the islet 1 β cells in women may be dependent upon autoantibodies rather than cytotoxic T cells. Sex hormones may also affect the expression of MHC antigens in vivo. Evidence of the genetic heterogeneity of Type I Diabetes demonstrate an association of the CD3 epsilon locus on chromosome I lq23 with the susceptibility to T1D in female, suggesting that this genetic region may harbour a new 'diabetogenic' gene (Wong et al., 1991).

2.1 Autoantigens/Markers of T1D

Glutamic acid decarboxylase (GAD) 65 is an early and important antigen in both human diabetes mellitus and in the NOD mouse. T cell responses to GAD65 occur early in diabetes pathogenesis, yet only one GAD65-specific T cell clone of the many identified could transfer diabetes. Transgenic mice on the NOD background expressing a T cell receptor (TCR)-specific for peptide epitope 286-300 of GAD65 were generated. These mice have GAD65-specific CD4 (+) T cells. Lymphocytes from these TCR transgenic mice proliferate and make INF gamma, IL-2, TNF-alpha, and IL-10 when stimulated in vitro with GAD65 peptide 286-300, yet these TCR transgenic animals do not spontaneously develop diabetes, and insulitis is virtually undetectable. CD4 (+) T cells, or p286-tetramer (+) CD4 (+) Tcells, from GAD65 286-300-specific TCR transgenic mice delay diabetes induced in NOD. This
suggests that GAD65 peptide 286-300-specific T cells have disease protective capacity and are not pathogenic (Tarbel, et al., 2002).

GAD65 contains a region of sequence similarity, including six identical residues PEVKEK, to the P2C protein of coxsackie B virus, suggesting that cross-reactivity between coxsackie B virus and GAD65 can initiate autoimmune diabetes. They have defined the MICA3 and MICA4 epitopes on GAD65 using the combination of phage display, molecular modeling, and mutagenesis and have provided compelling evidence for the involvement of the PEVKEK loop in the MICA3 epitope (Myerset al., 2000).

Plasmids containing cDNA for the rat 67- and 65-kD isoforms of glutamate decarboxylase (GAD-67 and GAD-65) were expressed in COS-cells, and lysates of [35S]methionine-labeled cells were used for immunoprecipitations. Certain epitopes are common to both isoforms. [35S]methionine-labeled GAD-65 was purified from COS-cell lysates and employed in a binding assay with 50 sera of patients with recent onset of Type 1 Diabetes mellitus. The antibodies against GAD-65 are present in a majority of patients with type 1 diabetes mellitus, along with autoantibodies against other islet cells. The radioligand-binding assay, which is convenient and sensitive for detecting GAD antibodies, may facilitate the screening of individuals with autoimmune islet cell disease (Velloso et al, 1993).

T1.5D is characterized by rapid loss of β-cell function (McDevitt, 2005), failure of oral agents, and acquisition of insulin requirement (Temple et al., 1989). These patients have islet cell antibodies (ICAs), GAD65 autoantibodies (GAD65Abs), or both, indicating an underlying autoimmune pathogenesis. GAD65Ab binding to the NH2-terminus of GAD65 or to GAD67, as observed in a group of GAD65Ab-positive T1.5D patients, is rarely found in early-onset Type 1 Diabetic patients. This difference in the binding pattern of GAD65Ab of
T1.5D patients compared with that of T1D patients supports the notion that the disease process may differ between these two types of patients. GAD65Ab epitopes in T1.5D patients differ from those found in T1D patients and other GAD65Abpositive phenotypes (Hampe et al., 2002).

**ICA69** adds another autoantigen to the family of identified islet target molecules, and by the manner of its identification and characterization large amounts of antigen are available for development of quantitative, convenient predictive assays for autoantibodies and analysis of the role of this molecule in diabetes autoimmunity, as well as its physiologic function. The open reading frame of the ICA69 cDNA predicts a 483-amino acid protein. ICA69 shows no nucleotide or amino acid sequence relation to any known sequence in GenBank, except for two short regions of similarity with BSA (bovine serum albumin). The ICA69 cDNA probe hybridizes with a 2-kb mRNA in poly (A+) RNA from human pancreas, brain, heart, thyroid, and kidney, but not with skeletal muscle, placenta, spleen, or ovary. Expression of ICA69 was also detected in cells and cell lines, as well as in tumoral tissue of islet cell origin. The native ICA69 molecule migrates to 69 kD in SDS-PAGE as detected with specific antibodies. Serum samples from relatives of IDDM (Insulin dependant Diabetes Mellitus) patients specifically reacted with affinity-purified recombinant ICA69 on Western blotting. The structural gene for ICA69 was designated ICA1. A homologue in the mouse, designated Ica-1 was mapped to the proximal end of chromosome 6 (within 6 cM of the Met protooncogene) (Pietropaolo et al., 1993).

**Islet cell Ag 512** (ICA512) is a recombinant human Ag that was isolated from an islet cDNA expression library by screening with human insulin-dependent diabetes mellitus sera and DNA sequencing of ICA512-3. A cDNA that contains a 1644 bp open reading frame,
suggests that it codes for a transmembrane protein having a single membrane-spanning segment and a cytoplasmic domain that is closely related to the first intracellular (catalytic) domain of the T cell protein tyrosine phosphatase, CD45 (Rabinet et al., 1994).

The protein tyrosine phosphatases (PTPs) IA-2 and phogrin (IA-2b) are also major autoantigens in T1D that possess common serological epitopes in their COOH termini. Two dominant epitopes were identified: one (AA 629–649) immediately adjacent to the transmembrane domain (aa 604–628) and the second (aa 755–777) lying in the NH2-terminal region of the conserved PTP domain. T-cells that are specific to either of these peptides and that could destroy islet tissue in vivo though spontaneous T-cell proliferative responses were observed in prediabetic female NOD splenocytes only on the AA 755–777 epitope. In NOD female mice immunized with the epitope peptide, intramolecular determinant spreading occurred from the aa 629–649 epitope to the aa 755–777 epitope but not in the opposite direction. Inferring that the initial T-cell response to phogrin is restricted to a small number of dominant peptides and that it subsequently spreads to other regions of the molecule, including those containing the major humoral epitopes that are highly conserved between IA-2 and phogrin, thus, owing to its importance in relation to T1D, this autoantigen was included in the study (Kelemen and Wegmann, 2001).

The HSP (Heat Shock Protien) 65 molecule, may contain a key antigenic epitope critical to the pathogenesis of IDD in NOD mice (Atkinson and Maclaren, 1993) In the autoimmune T1D, β-cell destruction is caused by glutamic acid decarboxylase antibody (GADA) and the heat shock protein (Hsp) is found to be involved in selectively regulating MHC class II presentation of the diabetes autoantigen, GAD. Experimental studies have shown that inactivation of HSP90 function inhibited MHC class II presentation of exogenous
and endogenous GAD presentation. Hence, the heat shock protein (Hsp90 α) was used as the target protein for the docking study in the present research.

IgG proinsulin autoantibodies (IgG-PAA s) found in a fraction of sera from patients with newly diagnosed IDDM suggest of a role for proinsulin as an autoantigen in diabetes (Kuglin et al., 1988).

In the mouse, two proinsulin isoforms coexist. Most studies point to proinsulin 2 as the major isoform recognized by T cells in the NOD mouse. It has been detected that NOD mice that are deficient for proinsulin 2 expression both within β cells and within the thymus develop accelerated diabetes points to the importance of proinsulin as an autoantigen in the NOD mouse. There is strong evidence in the human that VNTR alleles flanking the insulin gene are key determinants of diabetes susceptibility. They may control the β cell response to glucose within the islets of Langerhans and the expression of proinsulin in the thymus. In the mouse, there is no allelic variability in the 5′ VNTR flanking the insulin gene. Ins2−/− NOD mice may thus represent a new model that will allow study of the role of thymic expression of insulin in susceptibility to T1D (Thébault-Baumont et al., 2003).

SOX13: SRY (sex determining region Y)-box 13, also known as SOX13, is a human gene. This gene encodes a member of the SOX (SRY-related HMG-box) family of transcription factors involved in the regulation of embryonic development and in the determination of cell fate. It has also been determined to be a T1D autoantigen, also known as islet cell antibody (Li et al., 2005).

The GM2-1 autoantigen is not β-cellspecific within the islets. This molecule is a target of islet cell autoantibodies that bind to the whole pancreatic islet. This autoantigen is present in secretory granules similarly to other autoantigens in IDDM (insulin, carboxypeptidase H, 38-
kDa protein, etc.), suggesting that the autoimmunity to the components of this organelle may be central to the pathogenesis of the disease (Dotta and Previti, 1998).

Free fatty acids (FFAs) have been demonstrated as ligands for orphan GPCRs and have been proposed to play a critical role in physiological glucose homeostasis. GPR40 and GPR120 are activated by medium and long-chain FFAs, whereas GPR41 and GPR43 can be activated by short-chain FFAs. GPR40, which is preferentially expressed in pancreatic β-cells, mediates the majority of the effects of FFAs on insulin secretion (Rayasam et al., 2007). Dysregulation of FFA metabolism is responsible for insulin resistance and Type 2 Diabetes mellitus. The presence of some FFAs is essential for glucose-stimulated insulin secretion from pancreatic β-cells. However, if FFAs are chronically in excess, they can reduce insulin biosynthesis and secretion and induce β cell apoptosis. An elevated level of FFAs can lead to insulin resistance. Factors such as TNF-alpha and adiponectin, released from adipose tissue, can also modulate insulin resistance. Many interventions that are helpful in treating or preventing Type 2 diabetes, such as weight loss and certain pharmacological interventions, reduce circulating FFA concentrations to a greater or lesser extent (Wilding, 2007). Though the regulatory effect of FFAs occurs in part by their involvement as substrates in intracellular lipid signaling pathways; they also signal directly via seven transmembrane-spanning receptors (7TMRs; G protein-coupled receptors). Here, 7TMRs that are activated by FFAs and FFA amides are considered. Furthermore, identification and characterization of small molecule ligands for these FFA receptors (FFARs) that may be useful for treating patients with diabetes mellitus have been described (Costanzi et al., 2008).

Zinc transporter eight (SLC30A8) is a major target of autoimmunity in human type 1A diabetes and is implicated in type 2 diabetes in genome-wide association studies. The
type 2 diabetes nonsynonymous single nucleotide polymorphism (SNP) affecting aa325 lies within the region of highest ZnT8 autoantibody (ZnT8A) binding, prompting an investigation of its relationship to T1D. Diabetic autoimmunity which could be defined by a single polymorphic residue has not yet been documented. It argues against ZnT8 autoimmunity arising from molecular mimicry and suggests a mechanistic link between the two major forms of diabetes. It has implications for antigen-based therapeutic interventions because the response to ZnT8 administration could be protective or immunogenic depending on an individual’s genotype (Wenzlau et al., 2008).

Corticotropin-releasing factor 1 stimulates insulin secretion specifically at times of intermediate to high ambient glucose, and the Corticotropin-releasing factor 1-dependent phosphorylation of Erk1/2 increases with elevated glucose concentrations. This response is reminiscent of the actions of the incretins, which potentiate insulin secretion during such conditions with high glucose level. The effect of Corticotropin-releasing factor 1 on β cells, therefore is apparent to add yet another layer of complexity to the intricate network of paracrine and autocrine factors and their cognate receptors whose coordinated efforts can dictate islet hormone output and regulate β cell proliferation (Huisinga et al., 2010).

SNP, rs13266634 was found to be associated with T2D and with reduced insulin secretion in non-diabetic relatives. Because of its role in beta-cell function, this candidate SNP may confer increased susceptibility for beta-cell destruction in T1D. Genetic susceptibility for beta-cell dysfunction in the presence of autoimmunity may lead to accelerated progression and early manifestation of the disease (Gohlke et al., 2008). Intense immunosuppressive conditioning and autologous T-cell–depleted hematopoietic transplantation was safely used to treat these 10 patients with severe autoimmune disease. All
patients have demonstrated stabilization or improvement but durability of response remains unknown (Burtet et al., 1998).

Long-term treatment with isoleucine thiazolidide a Dipeptidyl peptidase IV inhibitor has been found to stimulate beta-cell survival and islet neogenesis in streptozotocin-induced diabetic rats. Therefore this research has considered Dipeptidyl peptidase 4 also termed CD26, – (PDB ID: 2RIP) for the docking experiments. This study is significant as the results suggest that DPP IV inhibitors may be useful for T1D (Pospisilik, et al., 2003).

A gain-of-function mutant of the lymphoid phosphatase Lyp (PTPN22) has recently been implicated with T1D and other autoimmune diseases, suggesting that small-molecule inhibitors of Lyp could be useful for the treatment of autoimmunity. Lymphoid phosphatase Lyp (PTPN22): PDB ID: 2P6X (Wu et al., 2009).

IL-7Ra blockade altered the balance of regulatory T cells and T(E/M) cells, hence promoting cell-extrinsic regulation and further increasing the threshold for diabetogenic T-cell activation. It appears that IL-7 contributes to the pathogenesis of autoimmune diabetes by enabling T(E/M) cells to remain in a functionally competent state and suggest IL-7Ra blockade as a therapy for established T-cell-dependent autoimmune diseases (Penarandaet et al., 2012).

Phosphoinositide 3-kinase p110delta in a therapeutic treatment mode, IC87114 treatment conferred prolonged protection from progression to overt diabetes in a number of animals. These findings suggest that PI3Kδ inhibitors could be useful for managing T1D (Durandet et al., 2013).

The CD80/CD86-CD28/CD152 costimulatory interactions transmit signals for CD4(+) T cell activation and suppression and are critically involved in the initiation,
progression, and reactivation of the immunopathology in autoimmune diseases. Hence blockade of the CD80 costimulatory axis has therapeutic potential (Rigby et al., 2008).

**HLA DMA and HLA DMB** are MHC class 2 molecules involved in the T1D pathway. Thus inhibiting or suppressing either of these would prove beneficial for the treatment of T1D. This was retrieved from the PDB, bearing the PDBID: 2BC4.

**HLA DP** is also an MHC class 2 antigen involved in the T1D pathway. This immune factor has also been considered in the present docking studies, having retrieved its Chain A: HLA class II histocompatibility antigen, DP alpha 1 chain and Chain B: HLA-DP2 beta chain linked with DRα peptide from the Protein Data bank, (PDB ID: 3LQZ)

Earlier studies declare that Immunotherapies that selectively suppress effector T-cells while permitting the development of natural regulatory mechanisms may have a unique role in establishing targeted long-standing immune protection and peripheral tolerance. Thus disruption of CD154, **CD28**, and LFA-1 pathways, can prolong allograft survival and prevent autoimmune disease in murine models and at times (re)establish immune tolerance (Dudhgaonkaret et al., 2009). Consequently, the TCR CD28 was included in this study. Its structure was downloaded from the PDB (PDB ID: 1YJD).

PTPN22, IL-7Ra, Phosphoinositide 3-kinase p110delta, CD80, CD28, HLA DP, HLA DMA and HLA DMB were used as protein targets in the present study in order to study the inhibitory effect of Curcumin, Alpha cyperone, Cyperene, Cyperotundone, Kobusone, Sujeonol and 2, 4- Dimethyl iso flavanone over these protein molecules by a series docking experiments. This step of the study was under taken especially because blocking of the above protein molecules by varous ligands have been shown to be beneficial in intervening the T1D pathway at various levels, and thus successfully prevent the disease progression.
2.2 Cytokines

INFγ is known to be associated with IDDM (Schroder et al., 2003). The expression of IFN-γ in the pancreas of transgenic mice has been shown to precipitate autoimmune diabetes. IFN-γproduced locally in the pancreas of transgenicanimals causes infiltration of lymphocytes and islet cell destruction. The other cytokines associated with the T1D are Tumour Necrosis Factor (TNF) Alpha, and Interleukin Gamma.

2.3 Stem-cell therapy

Diabetics using stem-cell therapy have been able to stop taking insulin injections for the first time, after their bodies started to produce the hormone naturally again (Rose, 2007). Most patients of T1DM became insulin free with normal levels of glycated hemoglobin A1c (HbA1c) during a mean 18.8-month follow-up who, were treated with the autologous nonmyeloablative hematopoietic stem cell transplantation (HSCT). Continued monitoring with C-peptide levels after stem cell transplantation showed preservation of beta-cell mass (Couri et al., 2009). Regarding to T1D, studies analyzing the therapeutic effects of stem cells in humans began in 2003 in the Hospital das Clínicas of the Faculty of Medicine of Ribeirão Preto - SP USP, Brazil. The Diabetes Control and Complications Trial (DCCT) was a 7-year longitudinal study that demonstrated the importance of the intensive insulin therapy when compared to conventional treatment in the development of chronic complications in patients with T1DM. This study demonstrated a reverse relationship between C-peptide levels (endogenous indicator of insulin secretion) chronic complications – that is, the higher the C-peptide levels, the lower the incidence of nephropathy, retinopathy and hypoglycemia. Henceforth, beta cell preservation has become an additional target in the management of T1DM (Couri and Voltarelli, 2009).
Transplantation of pancreatic islet cells into the portal vein can virtually normalize blood glucose levels, while circumventing a number of problems associated with pancreas transplantation (Tufveson, 2009). However, this approach, including the problems associated with cadaveric organ and cell harvesting, makes these options practicable for only a few T1DM patients. Generating surrogate insulin producing cells is feasible and rodent studies suggest that such cells may be adequate to treat T1DM. However, such cells do not have the sophisticated machinery to detect glucose levels that is possessed by native islet cells. Thus, their ability to steer insulin release in response to glucose levels has not yet been documented (Unniappan and Wideman, 2009).

Engineering regulatable insulin expression within a cell already equipped for regulated secretion may be efficacious for the treatment of insulin-dependent diabetes. By a regulatable cell-based system developed for delivery of insulin to treat diabetes, two intestinal cell lines in which human insulin expression is controlled by mifepristone were generated (Friedrich and Luft, 2009).

The transactivator gene encodes a chimeric regulator (GLVP) that consists of a VP16 activation domain, a Gal4 DNA binding domain, and a truncated progesterone binding domain that responds to mifepristone. This can be used to target the expression of the regulator to any particular cell or tissue of interest. Next, a target must be constructed. The target can be any gene with an SV40 polyadenylation signal placed under the control of a minimal promoter. Upon activation, the regulator then binds to the Gal4 sites and induces target gene expression. The regulator is inactive without mifepristone. When mifepristone is added, the activated regulator dimerizes and binds to the Gal4 DNA binding site that induces the target gene expression refined their cell lines and modified the gene-switch protein.
plasmid to replace the promiscuous tyrosine kinase promoter with promoter elements of nonsecretory cells. Thus, the resultant cells obeyed solely the mifepristone command in terms of insulin production (Cheung et al., 2000). Native K cells can be engineered (tumor-derived K-cell line), to produce human insulin by providing the cells with the human insulin gene linked to the 5'-regulatory region of the gene encoding glucose-dependent insulinotropic polypeptide (GIP) (Urbán et al., 2008).

Cotransplantation of sex-mismatched bone marrow cells (BMCs) and syngeneic or allogeneic mesenchymal stem cells (MSCs) supports pancreas tissue repair, stabilization of normal blood glucose and serum insulin level. MSC injection inhibit T-cell-mediated immune responses against newly formed beta-cells, helps to survive in this altered immunological milieu and caused the disappearance of beta-cell-specific T lymphocytes from diabetic pancreas thus BMCs and MSCs induce the regeneration of recipient-derived pancreatic insulin-secreting cells (Christiansen et al., 1981). Creation of an artificial beta cell was tested with respect to the glucose analyzer and insulin infusion modules of the Biostator system. The Biostator delivered 99% of the computed required insulin. Blood glucose results from the Biostator were compared with routine laboratory methods during long-term feedback control. The device enabled normal glucose tolerance to be achieved with smaller amounts of insulin (Lien and Zipris, 2009).

2.4 TLRs- Toll Like Receptors

In both the NOD mouse and diabetes-prone BB (BBDP) rat, TLR upregulation can suppress disease. In the BioBreeding Diabetes Resistant (BBDR) rat, however, diabetes induced by virus infection involves the upregulation of TLR9 pathways, and generic TLR upregulation synergizes with virus infection on diabetes induction. The TLR pathways
involved in mediating islet inflammation holds great promise for identifying new molecules that could potentially be targeted to specifically suppress the autoimmune process in individuals at high risk for disease development. The potential link between TLR up regulation and autoimmunity emphasizes the need for caution in using new therapies involving TLR agonists as vaccine adjuvants (Lien and Zipris, 2009).

Studies from animal models of T1D depict that the innate immune system plays a key role in early mechanisms triggering islet destruction. Mechanisms of pathways involved in innate immune subsets leading to human T1D is little known. Incubation of PBMCs in the presence of the TLR7/8 agonist R848 led to increased proportion of plasmacytoid dendritic cells (pDCs) expressing IFN-α. TLR4 activation induced a higher frequency of IL-1β expressing monocytes and a reduction in the percentage of IL-6 expressing myeloid dendritic cells (mDCs). The altered TLR responsiveness was not due to aberrant proportions of peripheral DC subsets and monocytes in the blood and did not correlate with altered hemoglobin A1c and the expression of diabetes susceptibility genes but could potentially be associated with enhanced nuclear factor-kappa B signaling levels of serum IFN-α2, IL-1β, IFN-γ, and CXCL-10 were elevated suggesting that altered innate immunity exists in mDCs and pDCs from T1D and raise the possibility that these alterations may be associated with disease mechanisms (Meyerset al., 2010). This work has identified different immune cell types in pancreatic beta-cell destruction, including CD4+ and CD8+ T cells, macrophages, dendritic cells, natural killer cells, and the dendritic cell subtypes. Indeed, by harnessing some immune cells, the pancreatic beta-cell destruction can be ameliorated or avoided altogether. The current findings suggest that solution to the puzzle requires identifying how these cell subtypes interact and are coordinated (Luft, 2010).
2.5 Adenosine Receptor agonists

The nonselective adenosine receptor agonist 5′-N-ethylcarboxamidoadenosine (NECA) prevented diabetes development in both MLDS (multiple-low-dose-streptozotocin) challenged mice and in cyclophosphamide-treated NOD (nonobese diabetic) mice. The effect of NECA was reversed by the selective A2B receptor antagonist N-(4-cyanophenyl)-2-[4-(2, 3, 6, 7-tetrahydro-2,6-dioxo-1,3-dipropyl-1H-purin-8-yl)phenoxy]acetamide (MRS 1754). The selective A1 receptor agonist 2-chloro-N6-cyclopentyladenosine (CCPA) and A3 receptor agonist N6-(3-iodobenzyl)-adenosine-5′-N-methyluronamide (IB-MECA) were less efficacious. NECA inhibited diabetes in A2A receptor KO mice and the selective A2A receptor agonist 2-p-(2-carboxyethyl) phenethyl-amino-5′-N-ethylcarboxamidoadenosine (CGS21680) had no effect in normal mice, indicating a lack of role of A2A receptors. NECA failed to prevent cytokine-induced β-cell death in vitro, but NECA strongly suppressed expression of the proinflammatory cytokines TNF-α, MIP-1α, IL-12, and IFN-γ in pancreata, endotoxin, or anti-CD3-stimulated splenic cells, and T helper 1 lymphocytes, indicating that the beneficial effect of NECA was due to immunomodulation (Nemeth et al., 2007). Adenosine acts as local modulator at four receptor subtypes named A1, A2A, A2B and A3 (ARs). Their signaling seems to be associated with pre/postconditioning cardioprotective and anti-inflammatory mechanisms. Identification of potent and selective agonists may represent a new therapeutic group Nucleoside based agonists, which are the result of modifying adenosine by substitution at the N6-, C2-positions of the purine heterocycle and/or at the 5′-position of the ribose moiety or combinations of these substitutions (Baraldi et al., 2008).
2.6 Stimulation of beta cell proliferation

Transcription factor E2F1 controls G1- to S-phase transition during the cycling of many cell types and is required for pancreatic beta -cell growth and function (Wu et al., 2001). Over expression of E2F1, either in vitro or in vivo, can stimulate beta cell proliferation activity. In vivo E2F1 expression significantly increases the insulin content and function of adult beta cells, making it a strategic target for therapeutic manipulation of beta cell function (Grouwels et al., 2010). Local pancreas donor retrieval with islet isolation and culture conditioning enabled an offer of islets for transplantation for 90% of consecutively processed pancreata. Isolated islets, during prolonged follow-up after implantation, secreted insulin and yielded metabolic control comparable with that achieved by best medical therapy. This portrays that a local multiorgan donor pancreas procurement program may serve a source for optimized isolation of purified viable islets for transplantation into patients with type 1 diabetes mellitus (Warnock et al., 2005)

2.7 INGAP

The Islet Neogenesis Associated Protein (INGAP) increases pancreatic beta-cell mass and potentiates glucose-induced insulin secretion. The main categories of genes modified by INGAP-PolyPeptide included several related with islet metabolism, insulin secretion mechanism, beta-cell mass and islet neogenesis. This explains for ten selected genes involved in growing, maturation, maintenance of pancreatic islet-cells, and exocytosis, i.e., Hepatocyte nuclear factor 3beta (HNF3beta), Upstream stimulatory factor 1 (USF1), K(+)-channel proteins (SUR1 and Kir6.2), PHAS-I protein, Insulin 1 gene, Glucagon gene, Mitogen-activated protein kinase 1 (MAP3K1), Amylin (IAPP), and SNAP-25. INGAP-PP also stimulated PDX-1 expression. It has been demonstrated that INGAP-PP enhances specifically the secretion of insulin and the transcription of several islet genes, many of them
directly or indirectly involved in the control of islet metabolism, beta-cell mass and islet neogenesis (Luft, 2010). Regenerating islet-derived 3 alpha, also known as REG3A, is a human gene that encodes a pancreatic secretory protein that may be involved in cell proliferation or differentiation. It has similarity to the C-type lectin superfamily (Barbosa et al., 2006).

INGAP is a member of the Reg family of proteins implicated in various settings of endogenous pancreatic regeneration. The expression of INGAP and other RegIII proteins has also been linked temporally and spatially with the induction of islet neogenesis in animal models of disease and regeneration. Furthermore, administration of a peptide fragment of INGAP (INGAP peptide) has been demonstrated to reverse chemically induced diabetes as well as improve glycemic control and survival in an animal model of T1D. Cultured human pancreatic tissue has also been shown to be responsive to INGAP peptide, producing islet-like structures with function, architecture and gene expression matching that of freshly isolated islets. Likewise, studies in normoglycemic animals show evidence of islet neogenesis. Finally, recent clinical studies suggest an effect of INGAP peptide to improve insulin production in T1D and glycemic control in T2D (Lipsett et al., 2007).

The INGAP is a pleiotropic factor enhancing islet neogenesis, neurite growth, β-cell protection, and β-cell function. Using an antibody to the N-termini of INGAP, it has been identified that immunoreactivity to INGAP occurs localized to the pancreatic endocrine cells in mouse. INGAP- and insulin-immunoreactive cells are mutually exclusive, with INGAP-immunoreactive cells being preserved after streptozotocin-mediated destruction of β-cells. Glucagon- and INGAP-immunoreactive cells co-localize, although respective antigen expression occurs in different intracellular locations. These data suggest that INGAP-
immunoreactive cells include α-cells; however, detection of single INGAP-immunoreactive/glucagon-negative cells indicates that this may not be exclusive (Taylor-Fishwick et al., 2008).

Induction of islet neogenesis by cellophane wrapping (CW) reverses streptozotocin-induced (STZ) diabetes. Administration of Iloitropin, a protein extract isolated from CW pancreata, causes recapitulation of normal islet ontogeny and reverses STZ diabetes, reducing mortality by 50%. We investigated the hypothesis that a novel gene encoding a constituent of Iloitropin was expressed in the hamster pancreas undergoing islet neogenesis. INGAP is a product of a novel gene expressed in regenerating hamster pancreas. INGAP gene is expressed in acinar cells, but not in islets. A synthetic pentadecapeptide, corresponding to a region unique to INGAP, stimulated a 2.4-fold increase in [3H] thymidine incorporation into hamster duct epithelium in primary culture and a rat pancreatic duct cell line but had no effect on a hamster insulinoma tumor cell line. A portion of human INGAP gene was cloned and appears to be highly homologous to the hamster gene. INGAP expression is increased in hamster pancreata in which islet neogenesis is experimentally induced by partial duct obstruction (Rafaeloff et al., 1997).

INGAP immunoreactivity was negative in pancreatic tissue of normal patients and of patients with pancreatic carcinoids or insulinomas. indicating that INGAP is a human cytokine, expressed only in pancreata undergoing islet regeneration in a topographic location compatible with stimulation of a protodifferentiated cell (Rafaeloff-Phail et al., 1998b). The development of the pancreatic anlage into the complex mature pancreas with components of endocrine, ductal and acinar structures is characterized by complex interactions between then is not yet known factors. Islet neogenesis associated protein (INGAP) is a putative islet cell
growth and differentiation factor whose expression is stimulated by experimentally induced islet neogenesis. It has been suggested that INGAP has a possible role in initiation of growth and differentiation of pancreatic endocrine cells (Rafaeloff-Phail et al., 1998a).

The possible relationship between changes in islet cell mass and INGAP-cell mass induced by sucrose administration to normal hamsters showed that a significant increase of INGAP-positive cell mass was observed at only 8 weeks when neogenesis was present, suggesting that this peptide might participate in the control of islet neogenesis. Thus, showing INGAP as an useful tool to treat conditions in which there is a decrease in beta-cell mass (Zotto et al., 2000)

Treatment of intra-islet precursor cells with pancreatic cell culture supernatant (PCCS) in vitro, led to the neogenesis of islets evidenced by dithiozone and insulin immunostaining. These substantiate the search for regenerative factors that converge towards the pancreas and its immediate surroundings (Kanitkar 2004). INGAP peptide improved defects on the peripheral sensory nervous system that characterize experimental diabetic neuropathy in mice, namely impaired thermal nociception and hyperphosphorylation of neurofilament proteins. The peptide enhanced nerve regeneration and induced structural protein and signal transduction changes characteristic of nerve regeneration, and enhanced mitochondrial metabolic activity (Tam et al., 2004). These research findings establish a remarkable, but yet to be utilised potential for the INGAP.

2.8 Various Methods of Treatments Available for Diabetes Mellitus

Metformin increased plasma active glucagons like peptide (GLP)-1[7–36NH2] concentrations in obese nondiabetic male patients, and it was suggested that metformin was a direct dipeptidyl peptidase (DP) IV inhibitor. Different antidiabetic mechanisms of metformin from DP IV inhibitors have revealed that metformin does not improve glucose tolerance via
an increase in circulating insulin levels (Hinke et al., 2002).

The C-terminal segment of the human insulin receptor α-chain (designated αCT) is critical to insulin binding as has been previously demonstrated by alanine scanning mutagenesis and photo-crosslinking. The technique of thermal-factor sharpening was employed to enhance the interpretability of the electron-density maps associated with the earlier crystal structure of the human insulin receptor ectodomain. The αCT segment is now resolved as being engaged with the central β-sheet of the first leucine-rich repeat (L1) domain of the receptor. The structure, together with isothermal titration calorimetry data of mutant αCT peptides binding to an insulin minireceptor, leads to the conclusion that putative “insulin-mimetic” peptides in the literature act at least in part as mimics of the αCT segment as well as of insulin. Photo-cross-linking by novel bifunctional insulin derivatives demonstrates that the interaction of insulin with the αCT segment and the L1 domain occurs in trans, i.e., these components of the primary binding site are contributed by alternate α-chains within the insulin receptor homodimer (Smith et al., 2010).

Chromium (Cr3+) an essential micronutrient may regulate blood sugar, because chromium deficiency is associated with diabetic-like symptoms, and chromium supplementation is correlated with increased glucose tolerance and insulin sensivity. Some Portuguese aromatic plants are utilized as tisanes by diabetic people as medicinal plants. Determination of chromium was performed by flameless atomic absorption. All the analyzed Portuguese medicinal plants contain chromium at the normal level for this element, but the plants used to prepare tisanes to help diabetic conditions contain higher levels than the others (Valdemar, 1998).

2.9 Plant drugs and their formulations- a promising future cure for the disease

Lots of chemical agents are available to control and to treat diabetic patients, but
total recovery from diabetes has not been reported up to this date. Alternative to these synthetic agents, plants such as *Allium sativum*, *Eugenia jambolana*, *Momordica charantia*, *Ocimum sanctum*, *Phyllanthus amarus*, *Pterocarpus marsupium*, *Tinospora cordifolia*, *Trigonella foenum graecum* and *Withania somnifera* provide a potential source of hypoglycemic drugs and are widely used in several traditional systems of medicine to prevent diabetes (*Jarald et al.*, 2008).

One of the etiologic factors implicated in the development of diabetes and its complications is the damage induced by free radicals and hence an antidiabetic compound with antioxidant properties would be more beneficial (*Modak et al.*, 2007). Many kinds of natural products, such as terpenoids, alkaloids, and flavonoids, phenolics, have shown to have antidiabetic potential. Particularly, schulzeines A, B, and C which were isolated from the marine sponge *Penares schulzei* (*Takada et al.*, 2004) radicamines A and B, (*Yu and Huang*, 2006) 2,5-imino-1,2,5-trideoxy-L-glucitol, -homofuconojirimycin, myrciacitrin IV, dehydrotrametenolic acid, corosolic acid (GlucosolTM), 4-(α rhamnopyranosyl)ellagic acid, and 1,2,3,4,6-pentagalloylgucose (*Zhang et al.*, 2009) have shown significant antidiabetic activities. Among active medicinal herbs, *Momordica charantia* L. (Cucurbitaceae), *Pterocarpus marsupium* Roxb. (Leguminosae), and *Trigonella foenum graecum* L. (Leguminosae) have been reported as beneficial for treatment of type 2 diabetes (*Jung et al.*, 2006).

Polyherbal therapy is said to be a current pharmacological principle having the advantage of producing maximum therapeutic efficacy with minimum side
effects.DRF/AY/5001 is a poly herbal formulation contains *Gymnema sylvestre*, *Syzygium cumini*, *pterocarpus marsupium*, *Momordica charantia*, *Emblica Officinalis*, *Terminalia belirica*, *Terminalia chebula*, *Shudh Shilajit* (Mandlik et al., 2008).

Neem leaf extracts improve the blood circulation by dilating the blood vessels and are demonstrated to be also helpful in reducing the need for hypo-glycaemic drugs. The decrease in blood glucose for the groups treated with combined extracts and bitterleaf only compared well (p<0.01) with chlorpropamide and non diabetic control, but not with neem alone. Determination of markers of hepatotoxicity in serum including GPT and GOT activities, total protein, albumin and urea indicated that, of the above four treatments, neem provides the best protection against hepatic dysfunction. In the group treated with combined extracts these alternate selective advantages of neem and bitterleaf were expressed as a positive synergy, hence more beneficial than individual treatments (Ebong et al., 2008).

Mucilages isolated from Malavaceous plants which show hypoglycemic activity have been found to have highly interesting chemical structure relating to a trisaccharide structural unit which offers interesting leads on structure-activity relationship.

Charantin (the non-nitrogenous neutral principle) and the polypeptide-p80 or plant (P)-insulin isolated from bitter gourd are found to possess antidiabetic activity.

As with pharmacological studies, most of the clinical trials on antidiabetic plants were also undertaken in a sporadic manner and not with any systematic approach. Among the many plants subjected to clinical trials, the major ones are *Allium cepa*, *Clerodendron phlomides*, *Cinnamomum tamala*, *Enicostemma littorale*, *Ficus bengalensis*, *Gymnema sylvestre*, *Momordica charantia*, and *Pterocarpus marsupium*.
It has been suggested that the hypoglycemic (and hypocholesterolemic) activities of gum guar are due to its dietary fibre content, causing a decrease in insulin demand and a progressive decrease in the HbAc levels (Satyavati et al., 1989).

A survey among the Afro-Trinidadians has revealed that bush medicines were used by 42% of patients surveyed and was used for diabetes by 24%. Bush medicine use was more frequent in Afro-Trinidadians and in those of mixed ethnicity than in Indo-Trinidadians. Patients taking bush medicines mentioned 103 different plants used in remedies. Among the 12 most frequently mentioned, caraili, aloes, olive-bush, and seed-under-leaf were preferentially used for diabetes. Vervine, chandilay, soursop, fever grass, and orange peel were preferentially used for other indications (Mahabir and Gulliford, 1997).

The aqueous extract of Syzigium cumini, commonly known as 'jamun', also resulted in decreased free radical formation in tissues studied. The decrease in thiobarbituric acid reactive substances (TBARS) and increase in reduced glutathione (GSH), superoxide dismutase (SOD) and catalase (CAT) clearly show the antioxidant property of the (Jamun seed Extract) JSEt. JSEt was more effective than glibenclamide in animals given 5.0 g/kg body weight (Prince et al., 1998). A significant linear relationship between antioxidant potency, free radical-scavenging ability and the content of phenolic compounds of leaf extracts has been observed (Ruan et al., 2008). A compound, mycaminose was isolated from Syzigium cumini seed extract. (50 mg/kg). The compound ‘Mycaminose’ and ethyl acetate and methanol extracts have been proved to possess anti-diabetic effects against STZ-induced diabetic rats (Kumar and Ilavarasan, 2008). Ethanol extract of seeds of Syzygium cumini seeds increased body weight and decreased blood sugar level on Alloxan diabetic albino rats. It also showed improved histopathology of islets. The blood sugar level that once dropped to
normal after feeding of the extract, continued to remain so even after discontinuing the extract feeding for 15 days (Singh and Gupta, 2008).

*Momordica cymbalaria* fruit powder has been established to manifest a significant reduction in fasting blood glucose levels in the treated diabetic rats, but no hypoglycaemic activity in the treated normal rats. *M. cymbalaria* treatment showed considerable lowering of serum cholesterol and triglycerides in the treated diabetic group. *M. cymbalaria* fruit powder possesses antidiabetic and hypolipidemic effects in alloxan-induced diabetic rats (Rao and Kesavulu, 1999).

It has been pointed out that Diabecon (D-400), a herbal formulation with hypoglycaemic effect, significantly reduced fasting (FBS) and two-hour postprandial blood sugar (PPBS) in newly diagnosed diabetics and in those already stabilised on antidiabetic medication. Oral hypoglycaemic agents could be omitted in 80% of cases, and the dosage could be reduced in the remaining, while maintaining equally good or better control of diabetes in patients already stabilised with these drugs. Insulin dosage could also be similarly reduced. No deleterious effects were observed on the liver, kidney or haemopoietic functions (Yajnik et al., 1993). The main ingredients of Diabecon (D-400) are *Gymnema sylvestre* 30 mg, *Eugenia jambolana* 20 mg, *Tinospora cordifolia* 10 mg, *Pterocarpus marsupium* 20 mg, *Momordica charantia* 20 mg, *Ocimum sanctum* 10 mg and Shilajeet 30 mg (Anturlikar et al., 1995).

It is an interesting fact that the antihyperglycaemic and antioxidant actions of ADD-199, at a dose of 100 mg/kg/day are comparable to those of the maximum daily therapeutic doses of glibenclamide (0.25 mg/kg) and metformin (50 mg/kg) (Okine et al., 2005).
Diamed, another polyherbal preparation, composed of the aqueous extracts of three medicinal plants (*Azadirachta indica, Cassia auriculata* and *Momordica charantia*) exhibited antihyperglycaemic action in experimental diabetes in rats with alloxan-induced diabetes by a significant improvement in glucose tolerance in the treated animals. The effect was comparable with 600 μg per kg glibenclamide (*Pari et al., 2001*).

Methanolic extract (75%) of *Terminalia chebula, Terminalia belerica, Emblica officinalis* and their combination named ‘Triphala’ (equal proportion of the above three plant extracts) are being used extensively in Indian system of medicine. They inhibit lipid peroxide formation and to scavenge hydroxyl and superoxide radicals. Oral administration of the extracts (100 mg/kg body weight) reduced the blood sugar level in normal and in alloxan (120 mg/kg) diabetic rats significantly within 4 hours. Continued, daily administration of the drug produced a sustained effect (*Sabu and Kuttan, 2002*).

Cogent db, a compound herbal drug, was investigated for its possible antidiabetic effect in alloxan-induced diabetic rats antihyperlipidemic effects in diabetic rats. It also prevents body weight loss in diabetic rats. There was a significant improvement in glucose tolerance in rats treated with Cogent db. A comparison between Cogent db and glibenclamide (600 μg/kg body wt.) showed that The antidiabetic effect of Cogent db was more than that observed with glibenclamide (*Pari and Saravanan, 2002*).

Episulin is a combination based on nine active scientifically proven herbs for their action in diabetes has been proven to be synergistically beneficial to a diabetic patient. This formulation contains an active principle Epicatechin derived from the bark of *Pterocarpus marsupium* which is a natural insulin mimetic. Each Capsule Contains *Pterocarpus marsupium, Momordica charantia, Eugenia jambolana, Cinnamom tamala, Trigonella*
Diasulin composed of ethanolic extract of ten medicinal plants regulates the activities of hepatic glucose metabolic enzymes, and acts upon on blood glucose, plasma insulin, tissue lipid profile, and lipidperoxidation in alloxan induced diabetes (Pari and Saravan, 2004). Diasulin, showed significant reduction in blood glucose, glycosylated haemoglobin and an increase in plasma insulin and total haemoglobin and better glucose tolerance. Diasulin also reduced activities of glucose-6-phosphatase and fructose-1,6-bisphosphatase in the liver, whereas the level of plasma insulin and hepatic hexokinase activity was significantly increased in alloxan diabetic rats. Decreased lipid peroxides and tissue lipids showed the antihyperlipidemic and antiperoxidative effect of Diasulin. Thus diasulin, controls the blood glucose level by increasing glycolysis and decreasing gluconeogenesis with a lower demand of pancreatic insulin (Saravanan and Pari, 2005).

Trace elemental analysis was carried out in various parts of some anti-diabetic medicinal plants using PIXE technique. A 3 MeV proton beam was used to excite the samples. The elements Cl, K, Ca, Ti, Cr, Mn, Fe, Ni, Cu, Zn, Br, Rb and Sr were identified and their concentrations were estimated. There were appreciable amounts of the elements K, Ca, Cr, Mn, Cu, and Zn, which are responsible for potentiating insulin action (Sarita and Raju, 2006).

Researchers suggest that curcumin-induced inhibition of IL-12 production in macrophages may explain its anti-inflammatory activity, and thus, curcumin may be useful in treatment of Th1- mediated immunological disorders such as T1D (Kang et al., 1998). In this research, the 3 dimensional docking of curcumin with all the selected targets was studied.
Callus culture of *A. marmelos* has as much potential in diabetes management as the original leaf extract and decreased blood sugar level in streptozotocin diabetic rabbits. The methanol extracts of the leaf and callus, together brought about the maximum anti-diabetic effect (*Arumugama et al., 2008*).

*Tinospora cordifolia* (Guduchi) is a widely used shrub in folk and ayurvedic systems of medicine. The chemical constituents reported from this shrub belong to different classes such as alkaloids, diterpenoid lactones, glycosides, steroids, sesquiterpenoid, phenolics, aliphatic compounds and polysaccharides (*Singh et al., 2003*).

The toluene fraction of *Coccinia indica* was the only active fraction. The active principles in this fraction were found to be triterpenes. The mechanism of action of these principle(s) is supposed to be due to their beta cell restorative properties against alloxan-induced damage (*Dhanabal et al., 2004*).

The oral administration of ethanolic extract of fruits of *Terminaliapallida* at a dosage of 0.5 g/kg body weight exhibited a significant antihyperglycemic activity in alloxan diabetic rats (*Rao et al., 2003*). The *Annonasquamosa* aqueous extract supplementation is useful in controlling the blood glucose level, improves the plasma insulin, lipid metabolism and is beneficial in preventing diabetic complications from lipid peroxidation and antioxidant systems in experimental diabetic rats; therefore, it could be useful for prevention or early treatment of diabetes mellitus (*Kaleem et al., 2006*).

Aqueous extract of leaves of 3 herbs (*Murraya koenigii*, MK; *Psidium guajava*, PG and *Catharanthus roseus*, CR) were used to test their antidiabetic activity in Streptozotocin induced diabetic albino rats orally once a day for 15 days. Aqueous extract of
leaves of MK, PG and CR at the dose of 500 mg/kg body weight was found to result in significant beneficial effects in various physiological/ histological parameters altered during diabetic manifestations and these effects are quite comparable with glibenclamide (Prasad et al., 2009).

_Hempedu Bumi_ and _Andrographis paniculata_ are used for anti-diabetes. Malaysian researchers are studying its anti-diabetic and antihypertensive properties (Aziz et al., 2005).

Crude Extract of _Cedrus deodara_ was blended with the various excipients for convenient to formulate as a unit dosage form. The two major active components were found to be alkaloids and terpenoids. The _Cedrus deodara_ wood extract was made into capsule with various pharmaceutical excipients and the subsequent evaluation revealed that the study had a vital role in the management of diabetes (Shivanand et al., 2009).

Herbal teas and infusions are traditionally used in the treatment of diabetes in Turkey, for their antidiabetic property. Ten aqueous herbal tea extracts were examined to arrive at a conclusion that none of the herbal teas showed antidiabetic effect on glucose diffusion using in vitro model glucose absorption. Ranking of the herbal teas with respect to their DPPH radical scavenging activity were green tea > peppermint > black tea > thyme > relax tea > absinthium > roselle > olive leaves > sage > shrubby blackberry (Buyukbalci and El, 2008).

‘Xiao-ke’ means diabetes in Chinese. It is estimated that more than 200 species of plants exhibit hypoglycaemic properties, including pumpkin, wheat, celery, wax guard, lotus root and bitter melon, hundreds of herbs and traditional Chinese medicine formulas have been reported to have been used for the treatment of diabetes mellitus, the use of these natural agents in conjunction with conventional drug treatments, such as a chemical agent or insulin,
permits the use of lower doses of the drug and/or decreased frequency of administration which decreases the side effects most commonly observed (Jia et al., 2003).

2.10 Databases of Antidiabetic Herbs

The active principles of many plant species with desired properties are isolated to cure both type-1 and type-2 diabetes. Sensing the importance of documenting such medicinal plants, a few databases were created. DiaMedBase (Babu et al., 2006), a database containing information of medicinal plants for diabetes available at http://www.progenebio.in/DMP/DMP.htm. Another database of 389 medicinal plants for diabetes containing information with regard to name, literature citation, active compounds and few related full text articles of the diabetes medicinal plants exhibiting hypoglycemic, antioxidant and antimicrobial effects christened as ‘A database for medicinal plants used in the treatment of diabetes and its secondary complications’ is available at http://www.autogeneralfilters.com/holycross/Home.html (Arulrayan et al., 2007).

2.11 The International and National Status of T1D Drug Research

The Juvenile Diabetes Research Foundation’s (JDRF) mission is to cure T1D and its complications through the support of research. The JDRF declares that ‘as of 2008, there is no known cure for T1D in modern clinical use’. Pancreas transplant is not practical (too few are available, and pancreas transplant is technically difficult). The JDRF is the major charitable organization in the USA and Canada devoted to T1D research (Voltarelli et al., 2007).

Islet transplantation is being practiced to a minor extent as a treatment for T1DM. In the period from 1999 to 2004, 471 patients with T1D have received islet transplants at 43 institutions worldwide.
The first successful trial of human islet allotransplantation resulting in long-term reversal of diabetes was performed at the University of Pittsburgh in 1990. Yetm despite continued procedural improvements, only about 10% of islet recipients in the late 1990s achieved euglycemia. In 2000, Dr. James Shapiro and colleagues published a report describing seven consecutive patients who achieved euglycemia following islet transplantation using a steroid-free protocol and large numbers of donor islets, since referred to as the Edmonton protocol. This protocol has been adapted by islet transplant centers around the world and has greatly increased islet transplant success. But, the requirement for immunosuppressive drugs contributes to the unsatisfactory nature of pancreas transplant as a cure.

Diamyd is the name of a vaccine being developed by Diamyd Medical. Injections with GAD65, an autoantigen involved in T1D, has in clinical trials delayed the destruction of beta cells for at least 30 months, without serious adverse effects. Patients treated with the substance showed higher levels of regulatory cytokines, thought to protect the beta cells. Phase III trials are under way in the USA and in Europe. Amylin Pharmaceuticals is working toward finding a cure, and has a drug in the market called Symlin (pramlintide acetate) that helps to cure T1D.

According to the The Indian Task Force on Diabetes Care in India, the crude prevalence rate of diabetes in urban areas is about 9% and around 3% in rural areas of the total population. This leads to a conclusion that at a conservative estimate, India is home to around 40 million diabetics and this number is thought to give India the dubious distinction of being home to the largest number of diabetics in any one country. In the year 2000, approximately 153.9 million were found affected with diabetes.
It is estimated that around 10% of the diabetic population have T1D, but, the actual affected population would definitely be much larger, because, in most cases, the cause of diabetes is not investigated and patients are not always screened for beta cell autoantigens.

In Chennai, Diabetes Department of the Voluntary Health Services stands out for the comprehensive free medicare of young people with T1D. They were the earliest to start the episode studies in both T1 and T2 DM in Chennai (Christen, 2007).

2.12 Conclusion of the review on the Autoimmune Diabetic Disease

This review shows that there are a number of targets like phosphoinositide 3-kinase p110 delta, HSP, phogrin, IL-7, CD28, CD80 and PTPN22 mutant lymphoid phosphatase that could be studied as potential drug targets for herbal medicine in order to arrive at a substantial cure for the autoimmune diabetic disease. The review has also revealed that blocking any one of the above targets could effectively intervent the T1 Diabetic disease pathway. Moreover in silico docking studies save a lot of time and cost in the journey of invention of a suitable drug which should be able to stop the immune destruction of the self (beta islet cells) insulin producing cells.