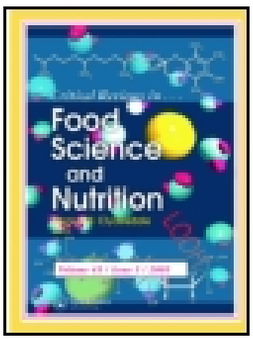

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Evidences for Diabetes and Insulin Mimetic Activity of Medicinal Plants: Present Status and Future Prospects

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Abstract

Diabetes mellitus (DM) is a considerable systemic metabolic disorder to exhibit various metabolic and cardiovascular disorders, mainly hyperglycemia. The global projected estimate of diabetes in 2030 will be about 439 million adults, out of which 300 million expected are of type-2 diabetes mellitus (T2DM). The present knowledge revealed responsible factors, occurrence and mechanism of these factors involved in the DM diseases. Hence, the aim of this review is to address and summaries the causes, plant resources, importance, present status and future programmes for diabetes control. The present review answer the contemprovery present questions raised in the scientific field on diabetes mellitus (DM). Two major problems are explained in detail about the autoimmune attack or dysfunction of β-cell and insulin resistance involved for Type 1 and Type 2 DM respectively. Though there are various approaches to reduce the ill effects of diabetes and its secondary complications, many preferred herbal formulations due to lesser side effects and low cost. For this reason still it is getting increased attention in

searching anti-diabetic medicinal plants for hot research and to develop targeted medicine. Recurrence of islet autoimmunity lesson from pancreatic islet cell transplantation to cure T1D was outlined. With this highlights, review summarizes the current knowledge on diabetes occurrence, factors (environmental and genetics), and types (I, II, gestation and secondary DM), antidiabetic plants, sources for insulin mimetic plant principle compounds and their target mechanism with current and future trusted research areas for controlling of DM was out lined.

Keywords

β-cell, Islet cells, Insulin resistance, DM, GLUT-4.

1. Introduction

According to World Health Organization (WHO) 65-80% of world's population in developing countries depends essentially on plants for their primary health care because of poverty and lack of access to modern medicine (Sharma et al., 2010). Many of the currently available drugs are plant-based, comprising of peptides that have a current hot source of biological compounds. The derivatives extracted for biological activities showed anti-tumor activity from *Inula helenium* L., *Hypericum perforatum., Chelidonium majus L., Inonotus obliquus* and *Equiseteum arvense L.,* (Tepkeeva et al., 2008); anti-HIV property from *Palicourea condensate* (Bokesch et al., 2001); anti-microbial activity of thaumatin-like proteins extracted from malting barley (Gorjanovic et al., 2007) and in different types of plants' proteins (Kim et al., 2009). In modern therapy for diabetes mellitus (DM), insulin and sulfonylureas provide relief from this disease. These are used either to reduce or prevent complication of the DM disease (Larner et al., 1985). Plants have been used since ancient times in the traditional medicine USED for the treatment of various diseases affecting human and animals and many of them are being

used and adopted in the world to cure DM (Nadkarni, 1954; Said et al., 1969; Satyavati et al., 1987).

The present paper explored the possible reasons for diabetes occurrence, some indigenous medicinal plants which have been pharmacologically evaluated for anti-diabetic property and future programmes to be pursued in this direction are enumerated..

2. Diabetes Mellitus (DM)

It is a metabolic syndrome usually caused due to the combination of hereditary and environmental factors, resulting in hyperglycemia due to defects either in the form of insulin secretion or insulin action in the body. Chronic hyperglycemia during diabetes causes glycation of body proteins that in turn lead to secondary complications affecting eyes, kidneys, nerves and arteries. Diet, exercise, use of oral hypoglycemic agents and insulin are the primary forms of treatment for diabetes. Currently available synthetic antidiabetic agents besides being expensive, produce serious side effects. Even though many therapeutic options are available, many herbal medicines have been recommended for the treatment of DM. Because, medicinal plants have the advantage of treatments with lack of any side effects compared to synthetic drugs. Traditional plants have been used throughout the world for DM therapy. History has shown that medicinal plants are being used in traditional healing around the world for a long time to treat diabetes. This is mainly because the herbal plants have hypoglycemic properties and other beneficial therapeutic properties as in scientific literatures (Donga et al., 2011). This review clearly shows the importance of herbal plants in the treatment of DM.

Ethnobotanists, throughout the world are collecting, documenting and conserving the medicinal plants especially indigenous, which are endangered and near to extinction. In the last two decades, many medicinal plants have been reported used to cure different common as well as severe diseases in several parts of India (Ayodhya et al., 2010). Diabetes mellitus is a complex metabolic disorder resulting from either insulin insufficiency in their action or less release of insulin. After digestion, the glucose reaches the blood stream where it is available for body cells to utilize as a main source of energy. Insulin is a hormone adequately secreted by beta cells in the pancreas and insulin is responsible to transport blood glucose into different cells of the body. If pancreas does not produce enough insulin, the regular body process will alter resulting in the glucose remaining in the blood and causing the person to be diabetic. Diabetes is a chronic disorder, metabolism in which a person has high sugar level in the blood because of insufficient insulin level in the body or the cells not responding to the insulin in the body (Fig. 1). This high level of blood sugar will turn the body to classical symptoms of polyuria (frequent urination), polydespia (increased thirst) and polyphagia (increased hunger).

2. 1. Types of Diabetes Mellitus

In body system due to insulin implication, body homeostasis and defects in beta cell of the pancreas leads to development of four major types of diabetes mellitus.

2.1.1. Type 1 diabetes

It is sometimes called Insulin Dependent Diabetes Mellitus (IDDM) or immune-mediated diabetes. It is caused by auto-immune reaction which attacks the insulin-producing β-cells (Fig. 2). This is rarely caused due to mutational defects in HLA region present in chromosome locus 6p21 commonly termed as IDDM1 (Nerup et al., 1974). This locus is more prone to cause many

auto-immune disorders of human including type 1 diabetes (T1D). Similarly, many gene variability responsible for T1D including Variable Number of Tandem Repeat (VNTR) polymorphisms accessed in the promoter segment of the insulin gene (Lucassen et al., 1993**).** PTPN22 is a relatively new gene responsible for T1D coding Lymphoid Protein Tyrosine Phosphatase (LYP) as a negative regulator of T-cell receptor signaling by gain of functional mutation (Smyth et al., 2004; Vang et al., 2005**).** Also the region of interleukin (IL)-2 receptor-α gene (IL2RA) allelic variation one of the important implicated factor in T1D (Qu et al., 2007) and CTLA-4 (cytotoxic T lymphocyte-associated protein 4) gene found in IDDM12 region (Ueda et al., 2003) and so on are responsible for T1D occurrence.

2.1.1.1. Environmental Triggers and its possible evidences for T1D

2.1.1.1.1. Cow's milk

Nearly 30 years ago, Borch-Johnsen et al. (1984) published the first report which suggested relationship between the breastfeeding and occurrence of autoimmune diabetes. Based on this observation now-a-days increase in evaluating the case-control experiments to know and predict the impact of cow's milk-based infant formula use during first 3-6 months baby exposing to developing autoimmune diabetes. Earlier researchers found, exposing baby's to cow's milk before the age of 3 months, will have increased risk of autoinduced diabetes (Gerstein, 1994; Norris and Scott, 1996). Cow's milk contains five major proteins such as caseins 70-80%, α-lactalbumin 5%, β-lactoglobulin 10%, γ-globulin 2%, and bovine serum albumin 1%. One theoretical mechanism explains the molecular mimicry of milk in body and developing auto-antigens for milk proteins when β-cell islet was identified (Kolb & Pozzilli, 1999). Another

concept by Vaarala et al. (1999) explained cross reactivity between β -cells and cow's milk proteins also discussed.

Based on above evidences and critical considerations it is impossible to explain cow's milk action by simple means of mechanism. One specialty regarding cow's milk is that, it is basically the first dietary foreign protein to fight against the newborn infants gut associated immune system. With this explanation certain diets having two basic routes for diseases progression. First, few diets give rise to biologically active components and destabilize in some genetically inactive individuals (Fukudome and Yoshikawa, 1992; Fukudome et al. 1997). Second, the dietary antigens elicit an immune response against diet antigens (Kolb & Pozzilli, 1999). Hence, attempts should be made to eliminate cow's milk in infant formulas and replace immune altering proteins by increasing zero reactive proteins in infant formula to escape from T1D.

This disease can strike during any age, but mainly seen in children or young adults. IDDM is characterized by deficiency in insulin production and requires daily insulin administration. The responsible factors for type 1 diabetes are difficult to predict. People having IDDM must need insulin injections every day to control glucose levels in the blood as per current knowledge.

2.1.1.1.2. Wheat proteins

In environmental view, till date two factors studied for diabetes are viruses and diet. Literature says, Enteroviruses may be involved (Vaarala et al., 2002), but yet no enterovirus has been identified (Viskari et al., 2002) from diabetic patients. Knowledge about epidemiological

evidence of infectious hotspots or traceable routes of infection is very poor (Patterson, 2001). There are conflict data with respect to the presence of candidate viruses in the pancreas or immune cells of diabetic patients (Juhela et al., 2000; Buesa et al., 1994). Still, there is no report mentioned about particular virus causing diabetes. Apart from wheat proteins (especially gluten received some attention (Volta et al., 1987)), one of the milk free diet food showing T1D in BioBreeding (BB) rats and Non-Obese Diabetic (NOD) mice. Experimental outcome showed, there is involvement of wheat storage globulin protein-1 (Glb1), having two subunits molecular mass of 49 kDa (pI 6.6) and 35 kDa (pI 6.9). But in diabetic children (not control), antibody binds to the protein having a mass of 50 kDa (pI 6.5). When the nature of this protein was determined using LC-MS/MS, it was found to have peptides homologous to both Glb1 and WP5212. In conclusion, immunoreactivity of the Glb1 responsible for occurrence of T1D by destructing the immune property. Hence, wheat protein may be involved in human T1D pathogenesis (MacFarlane et al., 2003; Hummel et al., 2002).

2.1.1.1.3. Cholecalciferol and the beta-cell

The Cholecalciferol, also called as Vitamin D (VD3, secosterol) is one of the important vitamin naturally synthesized by the skin from 7-dehydrocholesterol upon exposing to UV radiation (Mathieu et al., 2005) and also found in animal origin (Deluca, 2004). T1D is one of the autoimmune diseases by destruction of pancreatic insulin producing β -cells (Fig. 3). A number of epidemiological studies revealed the incidence of T1D when exposure to sunshine (Tuorkey and Abdul, 2010). T1D is also associated with imbalance of pro-/anti-inflammatory cytokines like interleukin-1 alpha (IL-1a), tumor necrosis factor alpha (TNF)-α, interferon gamma (INF-g), transforming growth factor beta1 (TGF-b1), interleukin-1 receptor antagonist

(IL-1ra) and IL-4, IL-6, IL-12 are main inflammatory mediators in the system. Preventing such an imbalance could reduce diabetes risk (Mathieu et al., 2005). The role of cytokines and some other inflammatory mediators influence the T1D and deficiency of VD in animal shows, impaired insulin release from β-cell cultured *in-vitro*. Whereas this abnormality can be tolerated by high VD concentration during culturing the islets. With these supporting data researchers conclude that VD is one of the candidates for diabetes free life (Bouillon et al., 2008).

2.1.2. Type 2 diabetes

Type 2 diabetes (T2D) is also called as Non Insulin Dependent Diabetes Mellitus (NIDDM). It shows altered insulin secretion, insulin resistance and accounts for about 90% of all cases of diabetes. T2D usually occurs after the age of 40, especially characterized by insulin resistance and impaired beta cell function. It is characterized by high blood sugar called hyperglycemia contributed by insulin resistance or reduced production of insulin from β-cell of pancreas.

2.1.2.1. Insulin resistance

In case of insulin resistance (IR), body cells do not use insulin but blood glucose requires more insulin to transport blood into cells (Fig. 4a). Still, it is not clear whether it is from insulin deficiency or IR. Obesity is supported to be one of the major factors causing to develop T2D and genetic factor imbalances the immune system to cause state of insulin resistance.

2.1.2.1.1. Genetic background

T2D incidence increasing in the world without knowing exact genetic variants for diabetes to control. A number of researchers point out as the genetic cause and refer to immune modulating and T2D causing genes. Based on research several genes have been identified

involved in T2D (Brunetti et al., 2014). For the incidence of IR, interaction of insulin with Insulin Specific Receptor (INSR) on insulin responsive cell surface is important. Pathophysiology of insulin action in the body's dependent on the INSR activation, followed by activation of particular signalling transduction. If there are defects in INSR gene, there is possibility of developing T2D. This gene mutation occurs only 3-4% patients with a genetic abnormality in a receptor protein, leading to the disease (Doria, et al., 2008; Ahlqvist et al., 2011). Recent investigation suggests that, there is High Mobility Group A1 (HMGA1) gene encoding architectural transcription factor associated with T2D, having the capability to alter the expression of INSR gene mRNA and intern protein involved signals the pathway of insulin interaction. HMGA1 is basically nonhistone protein binding to the AT-rich sequences of the DNA, providing stability and assembly of multicomponent enhanceosome complex (Bustin et al., 1996). Recently identified *c.*369del* novel genetic variant present on the 3' intron region of the HMGA1 mRNA contribute to curtailment of mRNA half-life and intern decline of HMGA1 gene expression. The effect of pathogenetic HMGA1 confirmed in mouse models, showing missing of HMGA1 expression covalently inhibit the INSR expression and insulin action in target cells. So only current literature available for supporting T2D pathogenesis is HMGA1 gene variants decreasing the expression of INSR in mice and human (Foti et al., 2005).

2.1.2.2. Diminished insulin production from β-cell

Beta cell dysfunction may lead to the pathogenetic condition in T2D. However, according to recent emerged evidences T2D condition mainly due to impaired dysfunction of β-cell (Fig. 4b). According to Butler et al. (2003) T2D characterized by insulin resistance, obesity and hyperinsulinemia; but now-a-days ignored the importance of β-cell in T2D condition. Decreased

mass of β-cell in T2D patients accounted approximately 40-65% (Defronz, 2009; Rahier et al., 2008; Yoon et al., 2003, Atkinson et al., 2014). However, even having advanced technologies many genetic studies are poorly understood to explain the functional mechanism associated with T2D incidence. These types of observations explain T2D status in populations which mainly deals with the defects in the factory of insulin production β-cells and also suffers from some environmental factors (Ingelsson et al., 2010).

2.1.2.2.1. Genetic defect

Reduction of insulin secretion from β-cell is linked to number of responsible gene variants. One functional gene candidate is identified and showed polymorphism in Insulin Receptor Substrate-1 (*IRS-1*) gene having responsible action in insulin interaction (Saxena et al., 2012). The new loci in large-scale gene-centric meta-analysis identified *SLC2A2* (solute carrier) gene encodes glucose transporter Glut2 expressed in the β-cell, kidney and liver as a glucose sensor to maintain homeostasis of glucose in the body (Permutt et al., 1989). Sun et al. (2014) reported other number of functional genes impaired in disease pathogenesis and approximately 70 loci associated with T2D have been identified. The current knowledge about genetics regarding T2D is not sufficient to prove clinical prediction about problems associated. These findings boost the research on previously reported Glut2 role in T2D. The data from animal studies yet to be prove in human and in clinical trials to support the β-cell dysfunction and its mass involved in T2D (McCarthy, 2010). Pharmacogenomics is an emerging field, aims to explore the molecular mechanisms of specific genes and drug efficiency to make decisions about gene dysfunction, drug selection, treatment and toxicology study. So far, small amount of heritabily associated genetic information identified and theses are under clinical trials in

preliminary stage to explore the relation associated with DM and its implications (Sun et al., 2014).

2.1.3. Gestational diabetes mellitus

Gestational diabetes mellitus (GDM) is another type of diabetes, occur during pregnancy due to high blood glucose level. It develops in one among 25 pregnancies worldwide and complications associated before and after the birth. But, GDM will considerably disappear after few months of pregnancy but offspring's are also at increased risk for developing T2D later in life. History says that even GDM definitely occurs in women within five to ten years after delivery. Gestational diabetes is formally defined as glucose intolerance with onset or first recognition during pregnancy and only diet modification is used to treat the GDM (American Diabetes Association (2008)). During 2005, one group started the experimental trials of Australian Carbohydrate Intolerance Study on Pregnant Women (ACHOIS) to establish the GDM and the complications associated. Outcome of ACHOIS stated that, diet programme improve the GDM linked woman's health with quality of life (Crowther et al., 2005).

2.1.4. Secondary diabetes

Secondary diabetes (SD) occurs due to genetic defects in β-cell function but in which the glucose level are controlled by successful iron depletion. SD may be permanent or it may be eradicated or reversed the condition of hyperglycemic condition. SD is a condition lead by some conditions like, Hemochromatosis, Glucagonoma, Pancreatectomy, Chronic pancreatitis, etc. and it requires insulin injection to keep blood sugar level under control. It's difficult for people who had pancreatectomy to produce own insulin. So, regular insulin injection is needed to control SD

as like T1D. Pancreatic dysfunction or insulin resistances caused by drugs are play a associated role in SD (Ganda, 1995).

Since ancient times, raw plants and their extracts were used to combat diabetes. Though pathophysiology of diabetes remains unclear and experimental data suggest that, pathogenesis of diabetes caused by free radicals generated during oxidative stress conditions to develop diabetic complications (Lipinski, 2001; Matteucci and Giampietro, 2000). Free radicals are potential agents to damage the basic constituents of cell Protein, Lipid and DNA leading to imbalance of cellular functions. Recent updated studies reveal that, free radicals can be controlled or neutralized by antioxidants to prevent diabetes was experimentally confirmed in animal models (Naziroglu and Cay, 2001). The etiological abnormalities in lipids and proteins impair body system to develop DM. Extracellular and lean proteins like laminin, collagen and elastin are the most probable targets of free radicals. These proteins intern modified to form glycoproteins due to the condition of hyperglycemia. The modified proteins in lens, vascular wall and basement membranes develop complications (Glugliano et al., 1996). Abnormalities in lipid metabolism release a oxidized lipoproteins like Very Low Density Lipoprotein (VLDL), Low Density Lipoprotein (LDL) and High Density Lipoprotein (HDL) in diabetes. In addition, Advanced Glycation End products (AGEs) also increase the vascular permeability by binding to specific receptors on macrophage.

Diabetes is a complicated multifunctional disease, demands a different therapeutic approach to prevent or cure T1D, T2D and its complications. Certain therapies are used for diabetes, but limitations like turning to hypoglycemic condition, gastrointestinal disturbances after chemo therapies and importantly high cost to buy (Dey et al., 2002). Now-a-days a major

part of research is going on to control diabetes in which, oxidative stress developed diabetes can be cured by suitable antioxidant therapy. Medicinal plants are being looked up once again for the treatment of diabetes. About number of traditional plants, only a small number of plants have received scientific and medical importance to assess their efficacy. Also World Health Organization (WHO) expert committee on diabetes recommended the use of traditional medicinal herbs to further investigation. The medicinal values of plants have been tested and testing by trial and error method by number of research groups worldwide. Till now herbal based medicines received attention because of their advantages over chemical drugs due to les cost, less side effect and cheap availability. Today also opportunities are still lots and open up for investigators for discovery of new herbal based medicines to treat diabetes and its complications.

3. Trials for Anti-diabetic Potentials of Medicinal Plants

Recent evidence suggests that, the plants and herbs are used as drugs in the form of synthesized analogue or derivatives to treat the blood sugar level or control the diabetic incidence. Many useful floral bioactive components used in pharmacology are entered to clinical trials to confirm their anti-diabetic effect *in-vitro* and *in-vivo* model systems. With this brief highlights, presenting a few of the flora having insulin mimetic activity. Details of diabetic properties of herbs with their recent reports in pharmacological and clinical hypoglycemic efficacy were described in Table 1. (Umesha, et al., 2013; Chauhan et al., 2010; Ezuruike and Prieto, 2014; Roja et al., 2014; Hegde et al., 2014). In Table 2, some of the plants having insulin mimetic or secretory properties are mentioned (Gray and Flatt, 1999; Alexiou and Demopoulos, 2010; Bharucha et al., 2011; Hannan et al., 2012; Patel et al., 2012; Panicker and

Gopalakrishnan, 2014) and also active chemical constituents their mechanism of action and available toxicity status are described as in following section;

3.1. Emblica officinalis

Family: Phyllanthaceae

Common name: Indian gooseberry

In Indian Ayurveda, *E. officinalis* plant parts like leaf, seed, fruit, bark and flowers were anciently used in control of diabetes by using herbal preparations. Without knowing the bioactive component, earlier they started formulations using different plant extracts. Recent study explained that plant has antioxidant, anti-diabetic property and significantly reduces the some other biochemical parameters like serum urea, Serum Glutamate-Pyruvate Transaminase (SGPT) and Serum Glutamic Oxaloacetic Transaminase (SGOT). Apart from these, plant extracts also showed enzyme activities like catalase, glutathione, glutathione peroxidase, superoxide dismutase in the liver and kidney of diabetic rats. The literature survey clearly suggests that, *E. officials* hydro methanolic leaf extract effectively normalize the impaired antioxidant status in streptozotocin induced diabetes study in dose dependent manner. Oral administration of ethanolic extract of seed powder decreased the blood glucose level and serum cholesterol level in alloxan induced diabetic rats (Nain et al., 2012).

3.2. Trigonella foenum-graecum

Family: Fabaceae

Common name: Fenugreek

Basically fenugreek seeds showed multiple benefits in patients with diabetic complications such as reduction in blood glucose level called hypoglycemia. Formulations have

tried a lot for control of diabetes found that, ethanolic extract of *T. foenum graecum* seed significantly decreased the blood glucose, SGOT, SGPT and serum cholesterol level in alloxan induced diabetic rats. Experimental approaches stared to know the bioactive component responsible for these activities present in fenugreek. Kulkarni et al., (2012) reported that, alkaloid extract of fenugreek dried seeds significantly increased serum insulin level of STZ induced hyperglycemic rats was documented.

3.3. Aegle marmelos

Family: Rutaceae

Common name: Stone apple

A. marmelos highlighted in Indian ayurvedic medicine used for the treatment of DM. Root bark decoction showed, hypoglycemic effect (1ml/100mg) in normal fasted rats. Anti-hyperglycemic activity was observed for leaf extract in treated diabetic rats with decreased blood urea and cholesterol (Ponnachan et al., 1993). Leaf extracts explored as known for insulin mimetic activity (Paulose et al., 1993). The aqueous leaf extract showed improvement in the functional state of pancreatic cells in streptozotocin (STZ) induced diabetic rats (Das et al., 1996) andacts as a hypoglycemic and antioxidant in diabetic male albino rats. Also fruit extract (125 and 250mg/kg) showed for anti-diabetic and antioxidant activity in STZ diabetic rats with partial restore of damaged pancreatic islets (Upadhya et al., 2004).

3.4. Allium cepa. Linn

Family: Amaryllidaceae Liliaceae

Common name: Onion

Onion leaves and bulb are important parts of the diet, cultivated throughout the India. Regular administration of 3% freeze dried onion powder showed anti-hyperglycemia, and antioxidant activity in STZ-diabetic rats (Babu et al., 1997). The callus from onion culture showed a potential hypoglycemic property of only onion bulb extract (Kelkar et al., 2001). Also showed potent antioxidant activity and lower the blood sugar level in normal rabbits of ether soluble fraction at 0.25mg/kg, orally. The onion juice in clinical trials used for the treatment of diabetic patients to control the blood sugar level. In diabetic rat model experiment, *A. cepa* juice showed antioxidant and anti-hyperglycemic effect. According to Kumari et al. (1995), S-methyl cysteine sulphoxide is a sulfur containing amino acid present in onion (at a dose of 200mg/kg for 45 days) exhibited as potent hypoglycemic drug in rat model was described.

3.5. Allium sativum

Family: Amaryllidaceae Liliaceae

Common name: Garlic

Allium sativum used as an important part of dietary ingredients all over India. In garlic, allicin (0.25mg/kg, orally) exhibited better hypoglycemic property in diabetic rabbits (Mathew et al., 1973). Different solvent system extracts like ethyl acetate, ethanol and petroleum ether extract (0.25mg/kg, orally) produced anti-hyperglycemic activity (Jain et al., 1975) in alloxan induced diabetic rabbits. In garlic, the antioxidant-allyl cysteine sulfoxide was isolated and used in the treatment of alloxan diabetic rats, showed almost to the same extent as insulin. One of the most important properties of the garlic is to stimulate pancreases for insulin secretion from ß-cells (Augusti et al., 1996). Also garlic extract (500mg/kg/day) proved to be effective for hyperglycemic condition (Thailiani et al., 2003). Oral administration of a laboratory diet

containing 0.05% of ajoene (derived from garlic) for 8 weeks has been observed to produce anti-diabetic effect in genetically diabetic KK-A(y) mice (Hattori et al. 2005). Kaleem et al., (2006) experimental observation found that, a key component of aged garlic S-allyl cysteine had potent antioxidant property and Accumulation of Advanced Glycation End Product (AGEP) formation was inhibited. Garlic also found that, bis (allixinato) oxovanadium (IV) is the most potent anti-diabetic agent used in type 1 diabetic mice on both intraperitoneal injections as well as oral administrations were confirmed by Adachi et al., (2006) studies.

3.6. Aloe vera

Family: Xanthorrhoeaceae

Common name: Aloe vera

Aloe vera is cultivated throughout India for its variety of medicinal properties. Vogler et al. (1999) clinical study reported that, oral administration of aloe might be a useful adjuvant for lowering of blood glucose in diabetic patients. According to Okyar et al. (2001), *A. Vera* leaf extract showed hypoglycemic activity on T1D and T2D rats and the effect being enhanced in T2D as compared with glibenclamide. Tanaka et al. (2006) clinical data revealed that, the administration of the five phytosterols from *A. vera* namely lophenol, 24-methyl-lophenol, 24-ethyl-lophenol, cycloartanol and 24-methylene-cycloartanol to severe T2D mice for 28 days decreased the fasting blood glucose levels 64%, 28%, 47%, 51%, and 55% respectively. Rajsekaran et al. (2006) study proposed that, oral administration of *A. vera* gel extract (300mg/kg b.w. per day for 21 days) in STZ-diabetic rats resulted in a significant reduction of fasting blood glucose and improved the plasma insulin level.

3.7. Andrographis paniculata

Family: Acanthaceae

Common name: Green Chirayta

Andrographis paniculata is an annual herb grows throughout India. This plant extract potentially acts as a hypoglycemic and anti-hyperglycemic in normal rats (Borhanuddin et al., 1994). Zhang et al. (2000) observation of *A. paniculata* plant extracts with dose dependent concentration and effectively reduced the fasting serum glucose level of STZ-diabetic rats. Moderate reduction in blood glucose level (52.90%) observed when hyperglycemic rats treated with 50mg/kg body weight aqueous extract of *A. paniculata*. This effect enhanced when the freeze-dried material used at a dose of 6.25 mg/kg body weight, then it reduced 61.81% blood glucose level was reported by Husen et al., (2004).

3.8. Annona squamosa

Family: Annonaceae

Common name: Sugar apple

Annona squamosa grow well throughout India and mostly used by tribal communities in northern India for the management of diabetes. The aqueous leaf extract exhibited hypoglycemic activity in streptozotocin-nicotinamide induced diabetic rats (Shirwaikar et al., 2004). Ethanolic leaf-extract (350mg/kg b.wt. orally 10-day) administration to STZ-diabetic rats has been shown to lower fasting blood glucose level to 73.3% (Gupta et al., 2004). Fruit pulp extract (2.5 and 5.0g/kg b.wt.) has been observed for improved glucose tolerance in alloxan diabetic rats (Gupta et al., 2005). Furthermore, Gupta et al., (2005) confirmed the fruit pulp (5g/kg b.wt.) brought down urine sugar, urine protein and glycol-hemoglobin in diabetic rabbits. This plant leaf

aqueous extract administration orally to diabetic rats for 30 days, significantly reduced the levels of blood glucose and increased the activity of plasma insulin and antioxidant enzymes.

3.9. Azadirachta indica

Family: Meliaceae

Common name: Neem

Azadirachta indica is one of the evergreen trees in India exhibited hypoglycemic and anti-hyperglycemic activity of aqueous extract in diabetic dog (Satyanarayan et al., 1978). Neem is one of the popular plant parts like leaves, oil and bark contents having biological activity. Hydroalcoholic extract showed anti-hyperglycemic activity in streptozotocin induced rats. Leaf extract of *A. indica* has been reported for the hypoglycemic activity in normal rats (Chattopadhyay et al., 1999). Crude ethanol extract (250mg/kg, for 2 weeks) potentially lowered the blood sugar level of alloxan diabetic rats (Kar et al., 2003). Ether extract of seed (2gm/kg b.w.) and seed husk (0.9gm/kg b.w.) restricted the oxidative stress in heart and erythrocytes caused by streptozotocin in diabetic rats (Gupta et al., 2004). Mukherjee et al. (2006) found that, beta-sitosterol is a steroid obtained from *A. indica*, may be responsible for its hypoglycemic activity. At the same time by Waheed (2006) clinical study on T2D, aqueous extract and alcoholic extract of *A. indica* at high dose for 14 days exhibited hypoglycemic activity. Apart from anti-diabetic activity, neem plant also properties like antioxidant, antimalarial, antibacterial, antifertility and hepatoprotective effects (Biswas et al., 2002).

3.10. Cinnamomum tamala

Family: Lauraceae

Common name: Indian Bay Leaf

C. tamala are widely cultivated in India, and used as a spice (Saxena et al., 2006). The aqueous leaf extract showed potential blood sugar lowering effect in glucose induced hyperglycemic rabbits at a dose of 500mg/kg. Udupa et al. (1980), powdered leaves oral administration (20gm for 15 days) exhibited the hypoglycemic effect in patients of T2D along with insulin released from pancreatic ß-cells. In a clinical study, this produced a hypoglycemic response in T2D patients (Chandola et al., 1980). Ethanolic extract (210mg/kg) of leaves induced the potential hypoglycemic effect in 18 hours fasted albino rats observed by Tripathi (1990). Alcoholic extract of leaves produced hypoglycemic activity in alloxan induced diabetic rats when administered orally for two weeks at a dose of 250mg/kg (Kar et al., 2003).

3.11. Momordica charantia

Family: Cucurbitaceae

Common name: Bittergouard

M. charantia growing in tropical areas of India used as a vegetable. From *M. charantia*, the charantin isolated and it has a mirror effect like insulin in lowering the blood sugar level of rabbits (Lolitkar et al., 1966) and also stimulating the pancreas to release insulin to block the glucose entry into the blood stream (Ng et al., 1986). Ethanolic extract (200mg/kg) of bitter gourd showed hypoglycemic activity in normal and streptozotocin diabetic rats; this was occurring possibly due to in liver inhibiting glucose-6-phosphatase, fructose-1, 6-biphosphatase and glucose-6-phosphate dehydrogenase activity stimulating hepatic cells (Shibib et al., 1993).

3.12. Ocimum sanctum

Family: Lamiaceae

Common name: Krishna Tulsi

It is an annual herb grown throughout India used for remediation purpose at home (Mukherjee et al., 2006). Alcoholic leaf extract of *O. sanctum* lowered blood sugar level in normal and glucose fed hyperglycemic diabetic rats and increase the release of insulin (Chattopadhyay, 1993). *O. sanctum* leaf content produced potent hypoglycemic effect in diabetic rats (Ravi et al., 1997). Hannan et al. (2006) experiment from leaf extracts like aqueous, butanol and ethyl acetate solvents acting as a stimulator of insulin secretion from rat pancreas was proved.

3.13. Pterocarpus marsupium

Family: Fabaceae

Common name: Indian Kino Tree

P. marsupium grown throughout India and used as folklore medicine (Mukherjee et al., 2006). Improved glucose tolerance was observed from aqueous and alcoholic bark extract (Pandey et al., 1975) fraction showed blood sugar lowering effect in pancreatic ß-cells damaged albino rats (Chakroborty et al., 1980). The bark having phytochemcial property which increased the cAMP in pancreatic islets intern increasing the release of insulin and converting the proinsulin to insulin in rats (Ahmad et al., 1991). Pterostilbene and marsupin are the two phenolic constituents present in the plant, responsible for decreasing the blood glucose concentration compared to metformin in diabetic rats (Manickam et al., 1997). The plant barks also having other potent biological activity like anti-cataract activity in alloxan induced diabetic rats (Vats et al., 2004).

4. Toxicological evidence and considerations

The administration of whole plant extracts or fractions consisting myriad of compounds, can elicit different biological actions human body and few of them showed toxic effect to the cells. These toxic effects are associated with certain parts of the plant. For example, the leaves of *Senna occidentalis* having hepato protective effects and are used traditionally for the treatment of liver disorders (Jafri et al., 1999). However, Vashishtha et al. (2009) reported the ingestion of toxins found in the seeds (beans) is the probable cause of acute hepato-myoencephalopath (HMP) in children. Apart from this, food scientist promoting the use of herbal products and ayurvedic formulations into health care medicine systems to avoid side effects of synthetic drugs in patient. The biologically active compounds from plant extract have proved for anti-diabetic property and some of the plants and there active components are listed in the table. 3.

Study of plant extracts for identification of possible bioactive phytochemical and selective constituent with respect to safety and less toxicity to the human cells is very important before it is used as a potential therapeutic agent. Previously, coumarins which are components of a wide range of plants and they were identified as hepato-toxic based on various studies carried out in rodents. However, studies have shown that, certain animal species are resistant to coumarin-induced toxicity. The7-hydroxylation metabolic pathway is the most favored in humans, leading to the formation of non-toxic metabolites. Whereas in rats, the most favored pathway is 3,4-epoxidation leading to the formation of hazardous metabolites (Felter et al., 2006). Evaluation of medicinal plants for potential active drug and its interaction in cell is equally important as like evaluation of efficacy and safety. Two types of herbal drug interactions are exist: pharmacodynamic interactions and pharmacokinetic interactions. Both the parameters

to be checked before drug to be released in the market. So, many naturally available bioactive molecules marketing today with specific target activity in the diabetic pathway. Few of them are listed in the table 3, with mechanisms of action (Satyavati et al., 1989; Noor et al., 2013; Ezuruike and Prieto, 2014).

However, a synergistic effect should not be assumed. It is sometimes advisable for patients not to take side effect implementing drugs due to negative drug interactions may occur. The water soluble fraction of okra fruits has been shown to decrease the absorption of metformin (Khatun et al., 2011). This results in decrease in the therapeutic concentration of metformin, which in turn may not bring the desired hypoglycemic effect in the patients (Ezuruike and Prieto, 2014).

5. Current status

Traditionally herbal treatment means, combination of multiple components of different plant sources and used as a medicines. Major advantage is, less toxic and free from side effects compared to synthetic drugs. Since the time of Charka and Sushruta diabetes mellitus is treated using many herbal medicines. Many used to treat known and unknown diseases even without proper knowledge on plant and their constituents present in the functions (Taylor et al., 2006). Several plants have been used and some of them in trail as a dietary adjuvant. Cucurbitaceae is a one of the well known plant family, having about 125 extant genera with different 960 species. Bnouham et al. (2006) considered, it is one of the very important plant family showing potent hypoglycemic effects.

Discovery of new drugs increasing every day from available herbal resources. The importance of *Cucurbitaceae* species has been markedly recognized in empirical control of

diabetes. *C. indica* is a creeper that grows in major parts of India. This plant has been used since ancient times for treating DM in Indian system of medicine known as ayurveda. Chopra et al. (1958) described that; *C. indica* is an 'Indian Substitute for Insulin'. Also, many reports discussed about this plant family regarding anti-diabetic medicine (Venkatraman and Pari, 2003). Because of the ostensible outcome, less side effects and cost effectiveness of natural medicines compared to synthetic drugs attracted the scientific bodies. That's why *Cucurbitaceae* family is widely acceptable choice of drug to treat diabetes even without their scientific backgrounds.

Honey is one of the nature's best insect-derived products without any side effect to human and also used as traditional, nutritional, spiritual, cosmetic, therapeutic and industrial value added product by manufactured by honeybees. Apart from these excellent properties, honey is a good source of active natural compounds like polyphenols for good physiological status. Unfortunately, there are only few current researchers investigating the nootropic, neuropharmacological effects and other cognitive functions of honey. Haron et al. (2014) recently reviewed the protective effect of honey against increased corticosterone level as well as ameliorate restraint stress-induced impaired pregnancy of rats was confirmed. Also, Gulfraz et al. (2011) reported the antimicrobial activity of various honey types reported from Pakistan. With this knowledge, we are proposed few most probable tasks to prove for diabetic free world in future. They are as follows,

5.1. Inhibition of glucose absorption by inhibiting enzyme kinetics

Postprandial hyperglycemia plays an important role in incidence of T2D. Since the recent research studies suggest that, the glycosylation by non-enzymatic reaction of various proteins cause development of chronic complications. Therefore, it is very necessary to control its level

via inhibiting the α-glucosidase enzyme activity. So researchers believed that, enzyme inhibition is an important strategy to manage the diabetes. The enzyme α-glucosidase is a member of the glucosidases acts on 1, 4-alpha bonds of starch give rise to disaccharides. This enzyme located in the brush-border surface of the intestinal cells and it is necessary for gastrointestinal absorption (Ramasubbu et al., 2004). In addition, α-amylase (also called ptyalin), found in both saliva and pancreatic secretions (Gao et al., 2008), having responsible action in breakdown of large starch macromolecule into smaller glucose and maltose units. Hence, successive research needed for inhibition of α-glucosidase and/or α-amylase enzymes. So, researchers are currently busy in searching for natural compound for inhibiting action of these enzymes and also need clinical trials for successive development of a drug against diabetes.

5.2. Enhancing glucose uptake and Glucose transporter upregulation

Currently one of the most promising goals for treatment of T2D is peripheral glucose uptake by multiple mechanisms intern that control blood glucose level. In this regard activation of the Glucose Transporter (GLUT) in liver (GLUT-2), adipocytes and skeletal muscles (GLUT-4), nuclear receptors, *viz.*, Peroxisome Proliferator-Activated Receptors (PPARs) are the gamma subtype, as well as increasing the release of positive adipocytokines, such as adiponectin. Cell membrane needs specific transporters to transport carbohydrates from lipid layer into cell. There are two different families of carriers, first one is sodium linked GLUT and second family has homologous transmembrane proteins. GLUT-1-8 conveys glucose transport depending on glucose-concentration gradients (Shepherd and Kahn, 1999). Of the entire GLUT family, GLUT-2 has a potential role in sensing glucose concentrations in the islets of langerhans and only GLUT-4 is insulin-responsive. GLUT-4 is sequestered intracellularly and is translocated to the

plasma membrane upon insulin stimulation. Therefore, decreased GLUT-4 gene transcription and translation reduces the insulin-mediated glucose uptake in diabetes condition (Kandror and Pilch, 1996). So, imperfect GLUT-4 function is one of the causative factors for insulin resistance (Berger et al., 1989**)**. From this point of view, researchers should look for genetics and functional physiology aspects through plants as a promising source. Because herbal active constituents play an important role in up-regulate GLUT-4 expression thereby it increase the translocation of this transporter could aid in the treatment of insulin resistance and hyperglycemia.

5.3. Glycogenolysis

One of the cornerstones in controlling the blood glucose level is regulation of "hepatic glucose output" by glycogenolysis and gluconeogenesis to know hormonal balance required to control blood homeostasis. Glucagon action is opposed to the insulin, but both the hormones should work in partnership with the body to keep blood glucose level in balanced condition. Same as insulin, glucagon is also secreted from the alpha cells of the pancreas which plays an active role in the body to regulate the utilization of glucose and fat. But glucagon responds when blood glucose level is very low, stimulating the liver to break down glycogen to be released into the blood as glucose. The latter process is maintained by levels of insulin (Gaw et al., 1998**)**, by stimulating glycogen synthase and inhibiting glycogen phosphorylase results in proper glycogen deposition in different tissues. Even presence of glucagon in people still getting diabetes because insufficient amount of insulin in body or body is not able to respond to insulin in T2D people. But in T1D hypoglycemic condition created by insulin because too much insulin inhibits the production of glucagon secretion from the islets of langerhans (Jiang and Zhang, 2003).

Consequently, researchers working for outcome of potential compounds from plants which induce the glycogen formation are considered as beneficial anti-diabetic agents in coming years.

5.4. PPAR-γ Nuclear receptor activation

The type II nuclear hormone belongs to the Peroxisome Proliferator-Activated Receptor (PPAR) family involved in regulation of carbohydrate, fatty acid and glucose metabolism. PPARs contain three isoforms specific tissue distribution and specific biological activity; there are α, β, δ and γ with two sub forms of PPAR-γ1 and PPAR-γ2. Generally receptors are involved in ligand dependent interactions; in that view antidiabetic thiazolidinediones (TZDs) is one of the potent PPAR-γ agonist. After stimulation by specific legends, which promotes the downstream target gene expression *via* their hetero demonization with retinoid X receptor (RXR) and their product binds to Peroxisome Prolixferator-Response Element (PPRE). Clinical data demonstrated that PPAR-γ agonists TZDs modulate glucose homeostasis by enhancing the peripheral glucose uptake through increasing GLUT-4 expression and translocation into adipocytes (Armoni et al., 2003; Omi et al., 2005). Apart from this, decreasing the hepatic glucose output which is also implicated in the pathology of numerous diseases including obesity, atherosclerosis and cancer. TZDs treatment with PPAR-γ reduces the serum glucose without increasing the pancreatic insulin secretion. So, combined treatment of TZDs with PPAR-γ is one of the best routes to treat the diabetic condition (Li et al., 2008).

5.5. Incretin and glucose balance

The gut hormone is one of new targets for the T2D management. Glucagon-like peptide-1 (GLP-1) or incretin is secreted as a riposte to the meal. This hormone stimulates glucose dependent insulin secretion to maintain glucose balance by different routes and counter acts the

glucagon secretion, delays gastric emptying and protects trophic effect on β-cells. But this hormone rapidly degraded by dipeptidyl peptidase- 4 (DPP-4), that inactivates glucose dependent insulin tropic peptide (GIP). So, the aim of pharmaceutical research is to inhibit DPP-4, to prolong the GLP-1 action, or identifying and designing compounds that can resist DPP-4. Also studying compounds having property like incretin-mimetic to simulate GLP-1 (exenatide) is demanded. In this regard, researchers should involve in clinical trials diamonding to find a better compound that could modulate incretin hormone (Scheen, 2007 and Scheen et al., 2007**)**.

5.6. D-chiro-inositol

D-Chiro-inositol (D-CI) is rare inositol isomer present in inositol phosphoglycans (IPGs) and call it is one of the second messenger like insulin. Insulin and other growth factors are responsible to release mediators from cell membranes. D-CI acts like insulin surrogate to exhibit anti-hypoglycemic effect *in-vivo* and also enhance the glucose incorporation into glycogen *in-vitro* (Fonteles et al., 1996**)**. According to Xia and Wang (2006), *Cucurbita ficifolia* plant may be a natural fairly high source of D-CI and having anti-diabetic character.

5.7. Antioxidants

In normal aerobic metabolism, free radicals are produced and inherently toxic to cells, which leads to built up body defense systems to quench them. These defense systems are either in the form of enzymatic action including catalase (CAT), glutathione-S-transferase (GST), superoxide dismutase (SOD) and glutathione reductase, or non-enzymatic, such as vitamins C and E, reduce glutathione molecule (Chandra et al., 1994). The free radicals are referred as Reactive Oxygen Species (ROS) able to overcome the endogenous defense systems to create a state of oxidative stress in the body. These ROS can bind to normal cellular components like

membrane lipids, proteins to unstable and attack nucleic acids to inactivate and resulting in the cellular oxidative damage. So that, oxidative stress play an important role in many diseases including DM, obesity, inflammation and cancer (Papas, 1996). Generally an antioxidant source like Nettle, Red Gram, Flaxseed, Sorghum Grains, Honey and Pomegranate (Manukumar et al., 2013a-c; Manukumar and Thribhuvan, 2014; Manukumar and Vanitha, 2014; Manukumar and Shruthi, 2014; Manukumar et al., 2014; Manukumar and Umesha, 2015) are good sources for some treatment of diseases and used in formulations of medicine. One of the independent risk factor to develop DM *via* "autooxidative glycosylation'' is development of ROS in the body. So, research is going still to start the plant based and synthetic drugs with high antioxidant property as favorable agents in diabetic patients to reduce diabetic risk (Sardesai, 1995**)**. Clinically, the herbal valuable antioxidant medicine *Silybum marianum* seed extract (silymarin) was confirmed in a randomized, double-blind, placebo-controlled and clinical study of 51 T2D patients (Garcia-Medina et al., 2011) showed better improvement in the glycemic profile of diabetic patients.

6. Past and future goals yet to be achieve

The global prevalence of diabetes is estimated to increase, from 4% in 1995 to 5.4% by the year 2025. According to literature, there are approximately 33 million adults with diabetes in India and likely to increase to 57.2 million by the year 2025. Nowadays phytomedicine are searched once again for diabetes treatment. Already so many drugs tried for diabetes are in clinical level. We believe that the list of medicinally important families and plants presented in this review is useful to researchers, as well as practitioners in any one of the other way. So, many reports have been published regarding hypoglycemic activity for bioactive compounds which are present in plants and those are extractable with different mixture of solvent phases. With the

critical global literature survey, there are 150 (Handa et al., 1989) plants and 343 plants from the different parts of the world have been addressed (Atta-ur-Rahman and Khurshid Zaman, 1989).

Enormous varieties of plants have been accessed and formulations were made specially for the treatment of diabetes and its associated medical complications. One of the major drawbacks with herbal formulation is that the active ingredients are not defined well. So, it is important to look at the active component and their molecular interaction, which will help to analyze therapeutic efficiency of the product and also to standardize formulated product. This type of knowledge needed to know the traditional medicinal importance in the diabetes treatment to peoples in the world. For searching of the optimal treatment for Type 2 diabetes may head to complications due to the complex pathogenesis of the disease. There are many researchers involved in improving the action of insulin on its target tissues, finding those compounds which have the abilities in improving the secretion of insulin by Beta-cells. In the past decade, several new oral agents had been discovered to control blood sugar in type 2 diabetes patients. These pharmacological agents work by different mechanisms with having their own adverse effects. Increasing population with diabetes, need huge requirement of effective remediation. The flora has a vast variety of medicinal plants, which are anciently used to treat diabetes. However, the popularity of the medicinally important and life saving flora are carefully assessed for ecological and medical purposes using different approaches, through toxicity assays. This type of different angular survey of informational research is first started for the basic knowledge and this may intern justifies the role of novel traditional medicinal plants having anti-diabetic property and its potentials to DM. Once again, for the treatment of DM many permissible and safe drugs have been derived from medicinal plants. On the basis of advantages

of plants derived compounds, metformin (oralglucose-lowering agent) was evolved to treat DM from *Galega officinalis*. After In-depth research on phytochemistry during 1920s at Europe comes to know that *G. officinalis* is rich in guanidine, having hypoglycemic property but too toxic for clinical use because of rich in guanidine then discontinued after insulin are commercially available (Rahul Gupta et al., 2008). Still, so much research ideas are going to implement for synthesizes the compounds having antidiabetic property (Thakur et al, 2014).

Some time overenthusiastic scientists jumping to address premature conclusions of plant drugs without confirmatory evidence on the identity of 'active principles' as well as a exact or novel mode of action. Such a movement is not appreciable to researchers in the field of science. Major hindrance in use of herbal medicine in modern era is lack of scientific and clinical data proving their efficacy and safety. There is a need of conducting clinical research in plant derived drugs and developing a reliable basis for standardizing biological activity and safety. Instead of trying to collection, writing of massive crude research oriented different active component in plants sources, it's better to start depth research for investigating the efficacy of the compound present in the plant, its mechanism of action and toxicity information is appreciated in the future (Rupesh kumar et al., 2014). Apart from above goals, another exiting goal in the field of molecular medicine is insulin (*INS*) gene target. *INS* is the insulin pre-proinsulin precursor encoded by the INS gene (Bell et al., 1980). Current research explaining about β-cell dysfunction cause T1D, but new hypothesis state that there is a differentiation of the specialized cells responsible for producing the insulin are reverting into simpler state reminiscent of stem cells. This effectively replaces the insulin into glycogen in the current hypothesis (Fig. 5 (Dor and

Glaser, 2013)). So, looking at this very important point of view, solve the *INS* gene function makes one of the strategies to overcome diabetic problems (Henriksson et al., 2005).

7. Current hot research

Still so many chemical methods are not reaching the goal of managing diabetes and peoples are searching for alternative way to manage the diabetes. Now-a-days stem cell research is the center of attraction for treatment of diabetes (Abdulazeez, 2013). Currently, University of Illinois at Chicago (UIC) performs kidney, liver, small bowel, pancreas and islet cell transplants. One of the ways identified by UIC's Division of Transplantation doctors and researchers and pioneer of Chicago Diabetes Project for conducting research on islet transplantation. Still so much clinical effort is needed to evaluate the diabetes to solve the problem (Alhabib et al., 2014).

7.1. Islet cells in capsule

A research group in Chicago Diabetes Project trying to transplant islet cells enclosed in biocompatible capsules (made from alginate). The technique used consists of the transplantation of isolated human pancreatic islets into the liver of a diabetic recipient. Mechanism of action involves, capsule having small tiny holes to block the immune cells coming in to destroy the islet cells, but it is not possible there because capsule allows only the nutrients to in and insulin to go out. This capsule also special character to prevent rejection. In above contest, planning a phase I/II clinical trial to transplant the encapsulated human islet in T1D patient. Academic center in U.S trying to answer the nature v/s human by transporting, the concept of microencapsulated islet into humans. This will work or not, we have to wait for some more days to get fruitful results. To prove this proposal and prove the controlling blood sugar level, offering millions of patients throughout the world for peoples living normal healthy life without complications to

prove this novel idea. With this vision researchers developing this kind of technological break in the field of medicinal science to cure diabetes (The Chicago Diabetes Project, http://www.uic.edu/com/surgery/transplant/).

8. Conclusion

With this comprehensive background, tagged paper highlighted a brief information of DM occurance, environmental triggers, list of antidiabetic plants used in the treatment of DM and various types of strategies going to adopt in future for control of DM. Plants are good sources of medicinal compounds, still many active compounds obtained from plants have not yet well characterized. More investigations for active components regard to the mechanism of action with antidiabetic and insulin mimetic activity was expected more in the future. Also future has to believe that, plant is safe but not all component, that's why toxicology study of those plants compounds should be elucidated with high concern of interest before consumption. Clinical trials are going on for diabetes control and one of the projects in Chicago diabetes center working and looking outcome of positive result on transplantation of islet cells enclosed in biocompatible capsules in diabetic patients to make diabetes free smile throughout the world.

9. Conflict of interest statement

All authors were declared of having no conflict of interest in the review studies. The authors alone are responsible for the content and writing of the paper**.**

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Table 1:List of plants used to treat Diabetes mellitus.

Plant part used	Name of the plant
Aerial parts	Cryptostegia grandiflora, Artemisia pallens, Bidens pilosa, Bixa orellana, Teramnus labialis, Bidens pilosa.
Bark	Anacardium occidentale, Berberis aristata, Ficus glomerata, Lagerstroemic speciosa, Pongamia pinnata, Ficus hispida, Ficus recemosa, Morus alba, Spathodea campanulata, Pterocarpus marsupium, Tecoma stans, Cinnamom zeylanicum, Blighia sapida, Hunteria umbellate, Hymenocardia acida, Ipomoea batatas, Morinda citrifolia, Persea Americana, Sarcocephalus latifolius, Senna alata.
Bulb	Allium cepa, Aloe sativum, Allii Cepa Bulbus.
Flower	Aegle marmelos, Catharanthus roseus, Cuminum nigrum, Musa paradisiacal, Clitoria ternatea, Morinda citrifolia, Punica granatum, Cassia auriculata, Gentiana olivier, Musa sapientum, Bryophyllum pinnatum, Calotropis procera, Curcuma longa, Momordica foetida, Senna alata.
Fruit	Lagerstroemic speciosa, Bhighia sapida, Cyamposis tetragonolobus, Lagerstroemic speciosa, Momordica charantia, Momordica, Cochinchinemis, Fructus Hordei Germinatus, Tribuluks terrestris, Ziziphus jujube, Carum carvi, Coriandrum sativum, Embellica officinalis, Juniperus communis, Momordica charantia, Xanthium strumarium, Solanum melongena, Sphenocentrum jollyanum, Spondias mombin, Tamarindus indica, Telfairia occidentalis, Terminalia catappa, Ximenia americana.
Leaves	Lagerstroemic speciosa, Morus alba, Adhtoda vasica, Aegle marmelos, Aloe barbadensis, Aloe vera, Althaea officinalis, Azadirachta

	indica, Cannabis indica, Capparis sepiaria, Catharanthus roseus, Ceiba pentandra, Eucalyptus globules, Galega officinalis, Gymnema sylvestre, Momordica charantia, Morus alba, Murraya koienigii, Olea europaea, Phyllanthus fraternus, Poterium ancisroides, Prunus persica, Rauwolfia serpentine, Tecoma stans, Aegle marmelos, Catharanthus roseus, Gymnema sylvestre, Herba Epimedii, Nymphaea stellata, Psidium guajava, Chloroxylon swietenia, Eucalyptus globulosus, Aloe barbadensis, Annona squamosa, Averrhoa bilimbi, Azadirachta indica, Beta vulgaris, Camellia sinensis, Cassia alata, Eclipta alba, Eucalyptus globulus, Euphrasia officinale, Ficus carica, Gymnema sylvestre, Gynura procumbens, Ipomoea aquatica, Mangifera indica, Myrtus communis, Memecylon umbellatum, Morus indica, Ocimum sanctum. Abrus precatorius, Acacia nilotica, Adansonia digitata, Aframomum melegueta, Ageratum conyzoides, Costus igneus Nak.
Rhizome	Nelumbo nucifera, Triticum repens, Anemarrhena asphodeloids, Atractylode japonica, Nelumbo nucifera Gaertn, Radix Clematidis, Radix Panacis Quinquefolii, Radix rehmanniae, Radix rehmanniae praeparata, Rhizoma Atractylodis, Rhizoma Pinelliae, Rhizoma Phragmitis,Zizyphus officinale, Adiantum lunulatum Burm, Rehmania glutinosa, Aristolochia albida, Curculigo pilosa, Curcuma longa, Zingiber officinale.
Roots	Lagerstroemic speciosa, Aconitum carmichaeli, Andrographis, Paniculata, Caeseria esculanta, Cassia auriculata, Catharanthus, roseus, Ceiba pentandra, Inula racemoma, Lagerstroemic speciosa, Launaea nudicaulis, Morus alba, Nymphaea nouchali, Oryza saliva, Panax ginseng, Panax quinquefolium, Rauwolfia serpentine, Thespesia populnea, Tribuluks terrestris, Xanthium strumarium, Aegle

	marmelos, Bridelia ferruginea Benth, Caesalpinia digyna Rottler, Celastrus paniculatus, Cichorium intybus, Cocos nucifera, Daucus carota, Erythrina variegate, Glochidion zeylanicum, Morus alba, Oriza sativum, Pedalium murex, Anthocleista djalonensis, Aristolochia albida, Bauhinia thonningii, Bauhinia tomentosa, Catharanthus roseus,
Seed	Datura stramonium, Eruka sativa, Lathyrus japonica, Solanum nigrum, Terminalia arjuna, Terminalia bellirica, Terminalia chebula, Trigonella foenumgraecum, Ventilago maderaspatana, Vigna mungo, Xanthium strumarium, Acacia Arabica, Azadirachta Indica, Bauhinia rectusa, Bougainvillea spectabilis, Caesalpinia bonducella, Cassia fistula, Centratherum anthelminticum, Cuminum nigrum, Cyamposis tetragonolobus, Glycine max, Leucaena leucocephala, Lithospermum erythrorhizon, Lupus albus, Momordica charantia, Mucuna pruriens, Acacia arabica, Lepidium sativum, Punica granatum, Chrysophyllum albidum, Citrus sinensis, Citrullus colocynthis, Cucumeropsis mannii, Detarium microcarpum.
Stem	Aloe vera, Cassia grandis, Ipomoea reniformis, Spathodea campanulata, Tinospora crispa, Vernonia anthelmintica, Allium cepa, Amaranthus spinosus, Catharanthus roseus, Amaranthus spinosus, Cosciniym fenestratum, Gongronema latifolium.
Tubers	Discorea batalas, Discorea dumentorum, Ipomoea batata.
Whole plant	Adiantum capillus-veneris, Aerva lanata, Brassica nigra, Cinnamomi cassia, Eragrostis bipinnata, Leucas aspera, Mimosa pudica, Stellaria media, Tinospora cardifolia, Withania somnifera, Abies pindrow, Achyranthus aspera, Ajauga iva, Aloe vera, Anacardium occidentale, Andrographis paniculata, Capsicum

	frutescens, Cryptolepis sanguinolenta, Enicostemma littorale, Ficus religiosa, Ageratum conyzoides, Anisopus mannii, Cassytha filiformis, Catharanthus roseus. Ipomoea batatas.

Source:(Bhushan et al., 2010; Sheu and Lai, 2012; Vadivel et al., 2011; Patel et al., 2012 and Ezuruike and Prieto, 2014)

Table 2: List of plants having insulin mimetic or secretary actions.

Sl.No.	Botanical Name of Plant	Family	Parts Used	Mechanism of action
1	Abies pindrow	Pinaceae	Whole plant	Insulin secretagogue activity
2	Acacia arabica	Mimosaceae	Seeds	Initiating the release of insulin from pancreatic beta cells.
3	Aegle marmelos	Rutaceae	Leaf, Fruit	Stimulate secretion of insulin by repair the injured pancreas.
4	Agrimony eupatoria	Rosaceae	Seed	Insulin releasing and insulin like activity
5	Allium Sativum	Liliaceae	Ripe Bulbs	Stimulated in vitro insulin secretion from beta cells.
6	Aloe vera	Aloaceae	Leaf pulp	Stimulation to release of insulin from pancreatic beta cells.
7	Aloe barbadensis	Liliaceae	Leaves	Mediated stimulating synthesis and/or release of insulin from the β cells of Langerhans.
8	Annona squamosa	Annonaceae	Leaves	Increased plasma insulin level
9	Asparagus racemosus	Liliaceae	Root	Stimulate secretion of insulin
10	Averrhoa bilimbi	Oxalidaceae	Leaves	Increase serum insulin level
11	Azadirachta	Meliaceae	Whole plant	Help to repair or

	Indica			regenerate the pancreas's beta cells, which play a crucial role in the production and secretion of insulin.
12	Biophytum sensitivum	Oxalidaceae	Leaves	Pancreatic β-cell stimulation
13	Bixa orellana	Bixaceae	Aerial parts	Increase plasma insulin concentration and increase insulin binding on insulin receptor
14	Bumelia sartorum	Sapotaceae	Root, Bark	Enhanced secretion of insulin from the pancreatic β cells.
15	Caesalpinia bonducella	Leguminosae	Seed, leaves	Good oral hypoglycemic agent.
16	Camellia sinensis	Theaceae	Fruit	Increase insulin secretion
17	Capsicum frutescens	Solanaceae	Whole plant	Increase insulin secretion and reduction of insulin binding on the insulin
18	Cinnamomum zeylanicum	Lauraceae	Bark	Elevation in plasma insulin level
19	Clausena anisata	Rutaceae	Root	Stimulate secretion of insulin
20	Coccinia indica	Cucurbitaceae	Leaves	Show glucose tolerance
21	Eucalyptus globulus	Myrtaceae	Leaves	Increase insulin secretion from clonal pancreatic

				beta line (BRIN-BD 11)
22	Ficus religiosa	Moraceae	Whole plant	Initiating release of insulin
23	Helicteres isora	Sterculiaceae	Root	Insulin sensitizing activity.
24	*Oreocnide integrifolia*	Urticaceae	Leaf	Significant insulin secretogogue, insulinomimetic effect and pancreatic beta cell regeneration.
25	Viscum album	Santalaceae	Leaf, Stem	Stimulate secretion of insulin.

Source:(Bhushan et al., 2010; Ayodhya et al., 2010; Chauhan et al., 2010; Singh, 2011 and Hannan et al., 2007)

Table 3:Current update on Biomolecules from medicinal plant against Diabetes.

Plant	Active molecule	Potential effect	References
Abrus precatorius	Trigonelline	Inhibited α-amylaseand α-glucosidase enzymes	Vadevil et al., 2011
Acacia nilotica	Pinitol	Hypoglycaemic Activity	Tanko et al., 2013
Allium cepa	Diphenylamine	Anti-hyperglycemic activity	Ogunmodede et al., 2012
Aloe vera	Pseudoprototinosaponin AIII and prototinosaponins AIII	Anti-hyperglycemic effects	Bnouham et al., 2006
Allium sativum	Allicin (diallyl thiosulfinate)	Anti-hyperglycemic activity	Corzo et al., 2007
Ananas comosus	Ferulic acid	Anti-diabetic activity	Xie et al., 2006
Azadirachta indica	Myricetin	Anti-hypoglycemic activity	Chattopadhyay, 1999
Azadirachta indica	Nimbidin	Hypoglycaemic Activity	Chattopadhyay, 1999
Bauhinia monandra	Rutin and Quercetin	Antihyperglycaemic effect	Aderogba et al., 2006
Bidens pilosa	Acetylenic glucosides	Decreased blood glucose level	Ubillas et al., 2000
Pterocarpus marsupium	(-)-Epicatechin	Anti-hyperglycemia	
and insulinogenic activity	Modak et al., 2007		
Blighia sapida	Hypoglycin A and B	Hypoglycaemic Activity	Chen et al., 1957
Bixa orellana	Isoscutellarein	Decreased blood glucose levels and increased plasma insulin levels	Terashima et al., 1991
Catharanthus roseus	Catharanthine	Hypoglycaemic Activity	Svoboda et al., 1962
Cymbopogon citratus	Geraniol, myrcene and citral	Decrease in fasting plasma gucose levels	Negrelle and Gomes,
2007			
Garcinia kola	Kolaviron	Decreased blood sugar	Iwu et al., 1990

Gongronema latifolium	α- and β-amyrin cinnamate	Anti- hyperglycaemic effects	Adebajo et al., 2013
Lawsonia inermis	Lawsone and gallic acid	Alpha glucosidase inhibitory effects	Sultana et al., 2009
Momordica charantia	P-insulin	Hypoglycaemic Activity	Paul and Raychaudhuri, 2010
Murraya koenigii	Mahanimbine	significantly decreaseblood glucose levels	Dineshkumar et al., 2010
Picralima nitida	Akuammicine	Hypoglycaemic effect	Oliver-Bever, 1986
Parkia biglobosa	Epicatechin	Hypoglycaemic Activity	Tala et al., 2013
Senna alata	Kaempferol and its 3-O gentiobioside	Decrease in blood glucose levels	Hennebelle et al., 2009
Zingiber officinale	6-, 8- and 10- Gingerols	Reduced blood glucose levels	Li et al., 2012

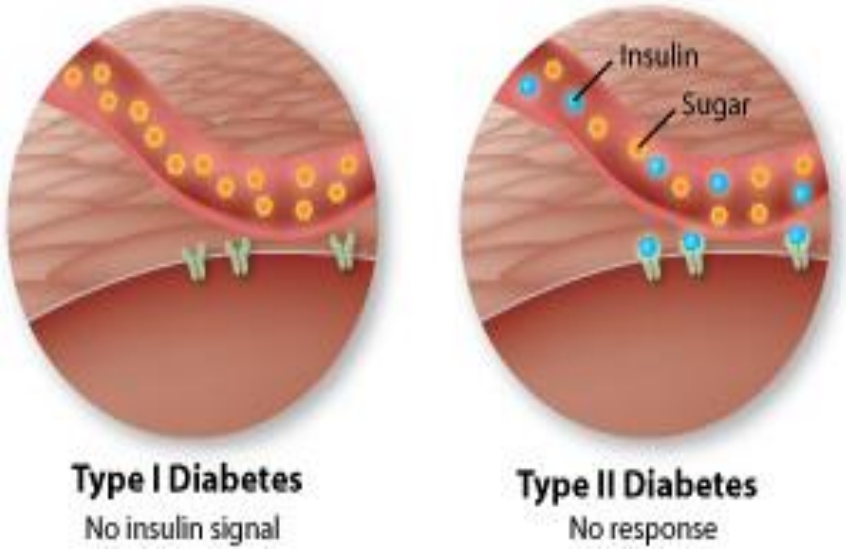

Fig. 1: Major types of diabetes condition. Picture showing blood stream having high levels of glucose in T1D due to because of shortage of insulin, or there is no insulin produced from β-cell cell. And in T2D even in presence of insulin also high in blood glucose level, because of insulin resistance. Derived Source: When Cell Communication Goes Wrong.

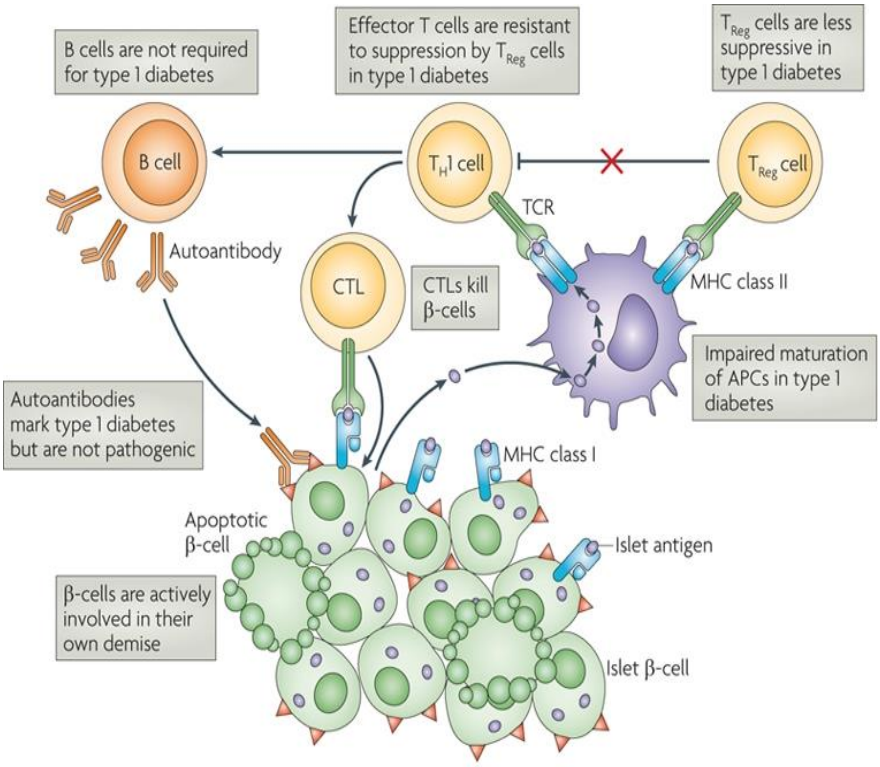

Fig.2: Auto immune rejection of β-cells impairs in Type 1 Diabetes. β-cell impair in the pancreases cause T1D due to insufficient release of insulin into the blood stream. Recognition of islet antigen to effecter T-cell suppresses the active form of β-cell and auto rejection because self degradation of insulin producing cell, finally β-cell become an apoptotic state. Source: Nature Reviews Immunology.

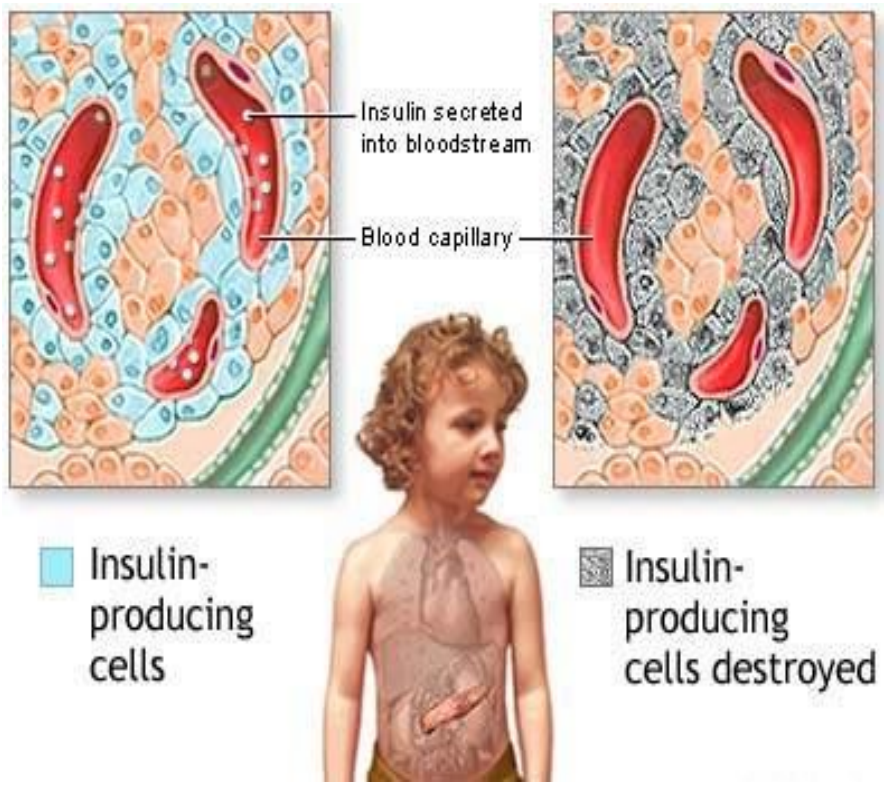

Fig. 3: Status of β-cell dysfunction. The illustration showing the T1D condition of insulin producing β-cell auto rejection status and insulin in blood capillary during active and dysfunctional condition. Source: The New York Times, Health Guide-Diabetes Type 1.

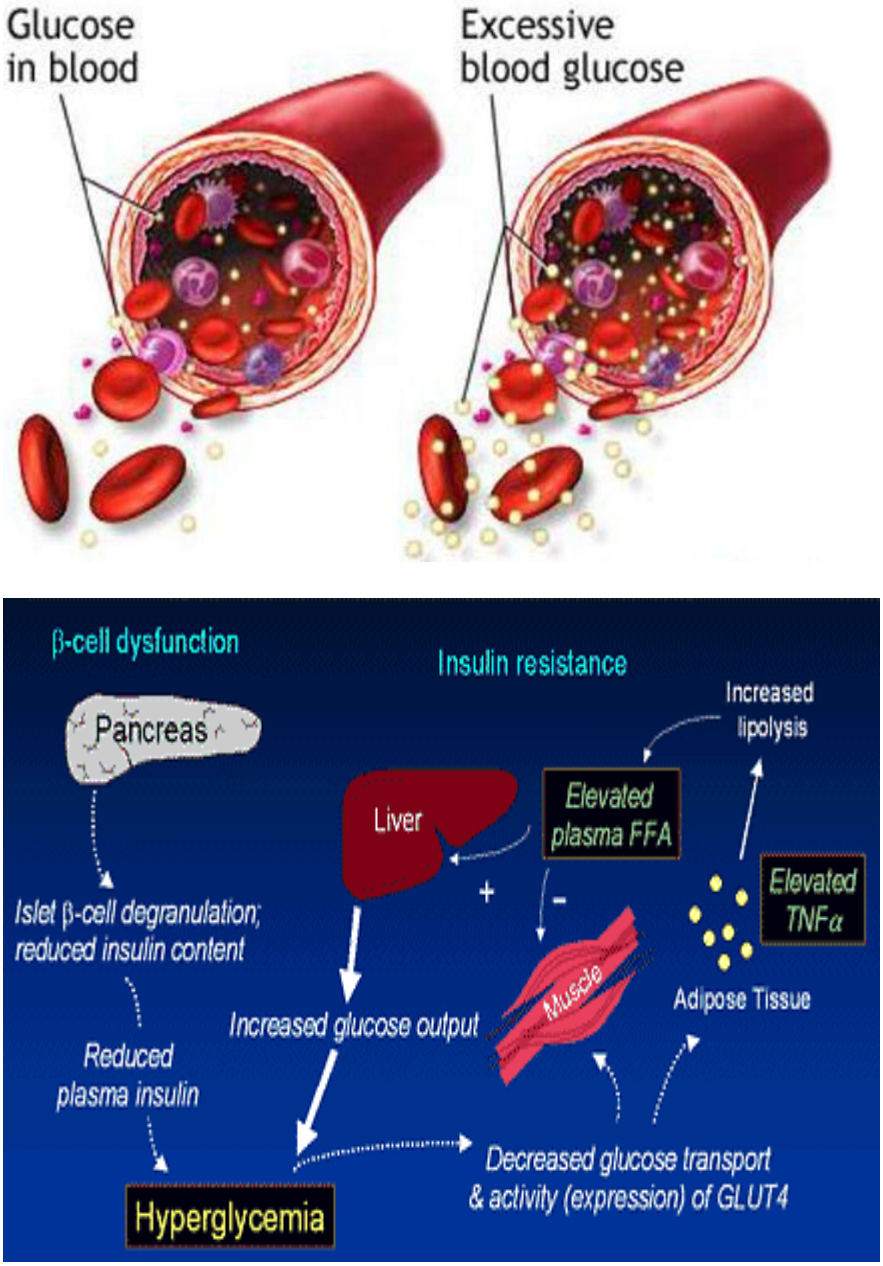

Fig. 4: a. Hyperglycemia condition during absence or resistance of insulin. In hyperglycemic condition, blood stream showing excessive blood glucose level, even in the presence of insulin in the blood due to insulin resistance status (fig. a.). A condition of high glucose in the blood altered when insulin content low or not working properly. During β-cell dysfunction there is a

reduction in production of insulin amount into blood intern there is an elevated amount of glucose in blood and state at which insulin presence also reduced transport of glucose into cells because the GLUT-4 transport mechanism at the inactive state is one of the issues to become insulin resistant (fig. b) make man T2D. Derived b. Glucose in blood in Type 2 diabetes. Source: a. Bio Hack Me-Blood Sugar, Insulin, and Ketosis. b. Goldstein, B. J., 2002.

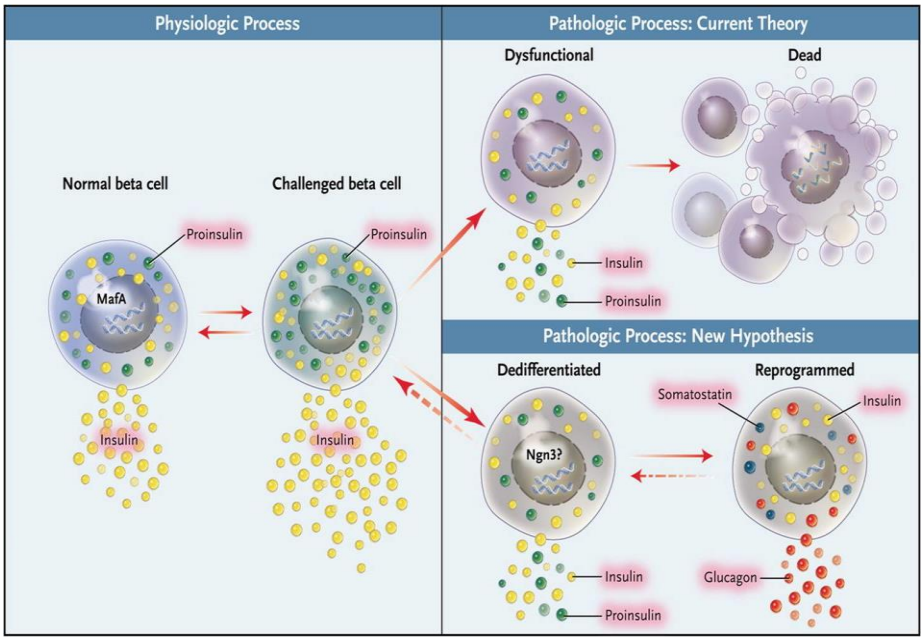

Fig. 5: β-cell in between Current theory v/s new hypothesis.Figure explains proper insulin production in normal cell when sufficient proinsulin present in the cell. Proinsulin condition can be varied through altering gene expression and it can be controlled. The two hypotheses evolved; first one says that the diabetic condition created by the β-cell dysfunction leads to the death of insulin producing cells. Second one is new hypothesis saying that, there is dedifferentiation of the β-cell again leads to reverting of the insulin secreting cell become stem cell to produce different types. This may be involved in the diabetic pathogenesis process. Source: Dor and Glaser, (2013).