



## Management of Diabetes and Complication: Herbal Therapies

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### Abstract

Diabetes mellitus is a universal metabolic disease characterized by means of hyperglycemia, hyperlipidemia, hyper aminoacidemia and hypoinsulinaemia. It leads to diminish in insulin, secretion and insulin action. Insulin is natural hormone secreted commencing the  $\beta$ - cells of pancreas which help out the cells to uptake glucose molecules from the blood flow. Diabetes mellitus is a chronic autoimmune disease related by selective damage of insulin-producing pancreatic  $\beta$ -cells. There are lots of multiple agents obtainable to control and to care for diabetic patients, although total recovery from diabetes has not been reported up to this time. Alternative in the direction of these synthetic agents, plants and nutrients supply a potential source of hypoglycemic drugs and are extensively used in some traditional systems of medicine toward prevent diabetes. Conventional systems of medicines with the perspectives of protection, efficiency, and quality will controls.

### 1 Introduction

Diabetes mellitus is a systemic metabolic disease characterize by hyperglycemia (increase glucose level), hyperlipidemia (increase lipid level), hyper aminoacidemia, and hypoinsulinaemia (decrease insulin level) it leads to reduce in insulin, release and insulin action<sup>1</sup>. human body do not produce or accurately us insulin, a hormone toward is required to exchange sugar, starches, and supplementary food interested in energy. Diabetes mellitus is characterized in continuous high levels of blood glucose (sugar). Human bodies have to maintain the blood glucose levels lying on a extremely narrow range which is done with insulin and glucagon. The purpose of glucagon is causing the liver to discharge glucose seeing as its cells into the blood for the making of energy<sup>2</sup>. Chronic hyperglycemia is associated through long-standing damage, dysfunction, and failure of dissimilar organs, especially eyes, kidneys, nerves, heart, and blood vessels<sup>3</sup>. It is estimated to facilitate in the year 2010 more than 200 million public worldwide will consist of DM and 300 million people will after have the disease in 2025<sup>4,5</sup>.

### 2 Etiology/Contributing factors

#### Type 1 Diabetes

1. Cause during the immune destruction of the beta cells of the pancreas.
2. Antibodies to islets cells and insulin are present on diagnosis.
3. Insulin secretion infrequently diminishes.
4. May nearby every age, but most common in early days and adolescence.
5. Insulin by injection is compulsory meant for survival

#### Contributing factors

1. Genetic predisposition
2. Environmental triggers (infection or else additional stress)

#### Type 2 Diabetes

1. Caused during insulin resistance in the liver and skeletal muscle, greater earlier than glucose production in the liver, over production of free fatty acids by fatty cells and relative insulin paucity.
2. Insulin secretion decrease through gradual beta cell failure.

3. Reductions in blood glucose levels frequently are achieved through changes in food eating and physical activity patterns. Oral medication and/or insulin injections are ultimately required.

#### Contributing factors

1. Fatness
2. Age (onset of puberty is allied through increased insulin resistance).
3. Not comprise of physical activity.
4. Genetic predisposition.
5. National/ethnic background (African American, Native American, Hispanic and Asian/Pacific Islander).
6. Conditions associated through insulin resistance, (e.g., polycystic ovary syndrome<sup>6,7</sup>).

#### 3 Types of mellitus (DM)

1. **TYPES 1 DIABETES:** (insulin-dependent diabetes mellitus, IDDM or immune-mediated or juvenile-onset diabetes): It is because by an auto-immune reaction universally the body's defense system destroys the insulin-producing  $\beta$ -cells. Community with type 1 diabetes turn out very little or no insulin. The disease repeatedly occurs in children or young adults. Patients totally depend on the exogenous insulin to control the levels of glucose in their blood. Genetic factors be thought to go on the main reason of it<sup>7</sup>.
2. **TYPE 2 DIABETES:** (non-insulin dependent diabetes mellitus, NIDDM or adult-onset diabetes): It accounts designed for at least 90% of all cases of diabetes. It is characterized by insulin resistance and relative insulin deficit. This occurs mainly appropriate to loss of functional  $\beta$ -cells. Type 2 diabetes is associated by means of very serious life cease complications<sup>8</sup>.
3. **GESTATIONAL DIABETES (GDM):** An appearance of diabetes consisting of high blood glucose levels throughout pregnancy. It develops in 2-4% of pregnancies generally in 2nd or 3rd trimester<sup>9</sup>.
4. **PREDIABETS:** This is body's declaration of warning sign to make some health change. Pre-diabetes is diagnosed following the level of glucose in the blood is higher than the normal limits but not quite high enough to diagnose as Type-2 diabetes<sup>10</sup> (Table:1).

#### 4 Insulin

Insulin plays an important role for the storage of excess energy in the body, Insulin is a natural hormone buried as of the  $\beta$ - cells of pancreas which helps the cells to uptake glucose molecules commencing the blood flow. Hence deficiency of insulin results

in the breakdown of glucose utilization by the cells and leading to its increased concentration in blood<sup>12</sup>.

**Table 1: Normal and Diabetes blood glucose level<sup>11</sup>**

	Normal	Diabetes
Fasting blood sugar	80-99 mg/dl	126 mg/dl and more than
Random blood sugar	80-139 mg/dl	200 mg/dl and more than
2hour glucose tolerance test	80-139 mg/dl	200 mg/dl and more than

#### Mechanisms of insulin

Coupled to several additional protein kinase signal

1. Pathways signaling all the draw near during PI 3-kinase and phosphatidylinositol (3,4,5)P3 (PI-3 kinase and protein kinase B/Akt).
2. Mitogen-activated protein kinases (MAPKinases).

NB: Both group 1 and 2 signals furthermore activate protein kinase C $\gamma$  and Protein kinase C $\zeta$ .

3. Possible interaction by kinases not coupled to IRS proteins<sup>13</sup>.

It have been suggested that the majority dominant is the first group (PI 3-kinase) which converts phosphatidylinositol 3,4 bisphosphate (PIP2) or [PI(3,4)P2] to phosphatidylinositol 3,4,5 triphosphate PIP3 or (PI 3,4,5)P3. These nucleotides act on the same time as anchors, binding down-line protein kinases to the plasma membrane and activating them. Insulin binds the first alpha subunits and lead to auto phosphorylation of beta subunits which extending cytoplasm by have bonds of two subunits, and induces converting active protein kinase<sup>14, 15</sup>.

#### Symptom of diabetes

1. being especially thirsty
2. urinating often
3. feeling extremely hungry
4. feeling very tired
5. losing weight underprovided trying
6. sores that heal slowly
7. dry, itchy skin
8. Approach of pins and needles in your feet
9. losing feeling in your feet
10. blurry eyesight<sup>16, 17</sup>.

## Causes

Diabetes as the two major causes of diabetes seem to be diet and exercise.

1. Obesity/overweight (especially overload visceral adiposity)
2. Excess glucocorticoids (Cushing's disorder or steroid treatment)
3. Excess augmentation hormone (acromegaly)
4. Lipodystrophy (acquired or genetic, associated with lipid accumulation in liver)
5. Auto antibodies to the insulin receptor
6. Mutations of insulin receptor
7. Mutations that cause genetic obesity (e.g., melanocortin receptor mutations)
8. Hemochromatosis (a hereditary disease that cause tissue iron accumulation)<sup>18, 19</sup>.

## 5 Pathogenesis of type 1 Diabetes

Type 1 diabetes mellitus is a chronic autoimmune disease linked through selective destruction of insulin-producing pancreatic  $\beta$ -cells. The onset of clinical infection represents the end stage of  $\beta$ -cell destruction primary to type 1 diabetes mellitus<sup>20</sup> (Fig 1).

1. Presence of immuno-competent and accessory cells in infiltrated pancreatic islet;
2. Association of susceptibility to disease with the class II (immune response) genes of the most important histocompatibility complex (MHC; human leucocyte antigens HLA);
3. Presence of atoll cell specific auto antibodies;
4. Alterations of T cell mediated immune regulation, in exacting in CD4+ T cell compartment;
5. The attachment of monokines and TH1 cells producing interleukins in the illness process;
6. Response to immunotherapy
7. Frequent occurrence of other organ specific auto- immune diseases in affected individuals or in their relatives members<sup>21, 22</sup>.

## 6 Pathogenesis of type 2 diabetes

In type 2 diabetes these mechanisms break down, among the consequence that the two most important pathological defects in type 2 diabetes are impaired insulin secretion throughout a dysfunction of the pancreatic  $\beta$ -cell, and impaired insulin action during insulin resistance<sup>23</sup>.

- i) Folks through normal glucose tolerance.

- ii) Chemical diabetes (called impaired glucose tolerance).

iii) Diabetes through minimal fasting hyperglycemia (fasting plasma glucose a smaller amount than 140 mg/dl).

iv) Diabetes mellitus in association through overt fasting hyperglycemia (fasting plasma glucose greater than 140 mg/dl)<sup>24</sup>.

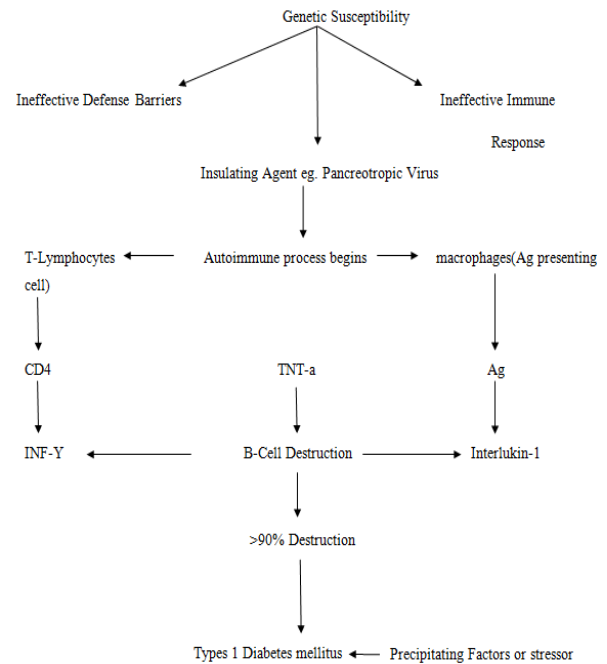


Fig 1: Pathogenesis of type 1 Diabetes mellitus

## 7 Complications in diabetes

The most important reason for this is because diabetes causes problems with the nerves as well as problems with the flow of blood during the blood vessels that supply energy for each organ. These two problems affect each organ in the human body<sup>25</sup>. So, when the blood glucose levels are not maintain because of unsuccessful or poor self-care, this can trigger the problems with blood vessels and nerves.

Diabetes is related with many complications similar to micro vascular (retinopathy, neuropathy and nephropathy), macro vascular (stokes, peripheral vascular diseases and coronary heart disease) and supplementary large blood vessel diseases similar to atherosclerosis<sup>26</sup>.

## 8 Diagnosis of disease

The blood glucose levels of a strong man are 80mg/dl on fasting and uptown 160mg/dl in the post prandial state. Diabetes mellitus is characterized by recurrent or persistent hyperglycemia and able to be diagnosed by any one of the subsequent tests:

1. A fasting plasma glucose (FPG) test: events blood glucose in a person who has not eat everything for at least 8 hours. (>162 mg/dL).

2. An oral glucose tolerance test (OGTT): measures blood glucose subsequent to a person fasts at smallest amount 8 hours and 2 hours after the person takes 75g oral glucose load(>200mg/dL).
3. A casual plasma glucose test: also called the person individual tested last (200>mg/dL).
4. Impaired Glucose Tolerance (IGT): To replace this grouping of intermediate hyperglycemia by an generally risk assessment for diabetes, cardiovascular disease, or both, which include a measure of glucose as a uninterrupted variable<sup>27-28</sup>.

**Table 2: Herbal drugs and mechanism of action**<sup>34-64</sup>

Botanical name	Common name	Family	Part used	Chemical constitute	Mode of action
<i>Momordica charantia</i>	Karela	Cucurbitaceae	Fruit	Charantin, sterol	Decrease blood glucose level.
<i>Aloe barbadensis</i>	Aloe vera	Aloe barbadensis	Whole plant	Aloe-emodin, aloetic-acid, anthranol, aloin A and B	Stimulation of synthesis and liberate of insulin beginning pancreatic beta cells.
<i>Azadirachta india</i>	Neem	Meliaceae	Whole plants	Azadiracthin, nimbin, nimbinin, nimbolide, nimbilic acid.	decrease blood glucose level by regeneration of $\beta$ cells.
<i>Allium sativum</i>	Garlic	Alliaceae	Bulbs	S-allyl cystein sulfoxide (SACS), allin.	Increased the insulin approximating activity of plasma.
<i>Aegle marmelos</i>	Bael	Rutaceae	Leaf	aegelin & aegelinin and marmesin	Increases utilization of glucose, direct stimulation of glucose uptake, conciliation of enhanced insulin secretion, Account for the hypoglycemic potential.
<i>Eugenia jambolana</i>	Indian goosebery jamun	Myrtaceae	Seed powder	Tri-terpenoids, tannins, gallic acid, and oxalic acid	It exhibits normoglycemia and better glucose Tolerance.
<i>Zingiber officinale</i>	Ginger	Zingiberaceae	Leaves	6-Gingerol, tannins, polyphenolic, flavonoids.	Decrease blood glucose level.
<i>Allium cepa</i>	Onion	Liliaceae	Bulb	Sulfar containing amino acid s methyl cysteine sulphoxide	Lowers blood glucose level, potent Antioxidant activity, which may account for the hypoglycemic potential.
<i>Mangifera indica</i>	Mango	Anacardiaceae	fruit	Mangiferin, mangifera	Hypoglycemic action.
<i>Ocimum sanctum</i>	Tulsi	Labiatae	whole plant	eugenol and caryophyllene, rosmarinic acid and ursolic acid	created potent hypoglycaemic and hypolipidemic effect.
<i>Tinospora cordifolia</i>	Gaduchi	Menispermaceae	Root	Alkaloids, diterpenoid lactones,	Decreases the blood glucose intensity and increases glucose

				glycosides, steroids, tolerance. Sesquiterpenoid,	
<i>Acacia arabica</i>	Babhul	Mimosaceae	bark	galactopyranose, L-arabofuranose and aldobionic acid 6- -d- glucuronosido-d- galactose	hypoglycemic effect, initiating release insulin from pancreatic beta cells.
<i>Cinnamomum</i>	Indian Cassia	Lauraceae	Bark	Cinnamaldehyde, eugenol	Promoting the insulin release from the undestroyed $\beta$ -cells.
<i>Swertia punicea</i>	Chirayita	Gentianaceae	Whole plant	Methyl swertianin and Bellidifolin	$\alpha$ -glucosidase inhibitors.

**Table 3: Allopathic drug and mechanism of action**<sup>65-72</sup>

Drug	Mechanism of Action
<b>Insulin secretagogues</b>	Attach to an ATP-sensitive $K^+$ ( $K_{ATP}$ ) channel, slow down a boost, hyperpolarizing efflux of potassium, depolarization open voltage-gated $Ca^{2+}$ channels, better secretion of (pro)insulin.
Sulfonylureas (glibenclamide, glipizide, glimepiride)	
<b>Insulin sensitisers:</b> Biguanides (metformin)	Glucose-lowering achieve by inhibiting hepatic gluconeogenesis and opposing the act of glucagon. The inhibition of mitochondrial complex I consequences in defective cAMP and protein kinase A signalling in respond to glucagon. Inspiration of 5'-AMP-activated protein kinase.
<b>Thiazolidinediones</b> (pioglitazone, rosiglitazone)	Binding to the PPAR- $\gamma$ receptor through the purpose of expressed predominantly in adipocytes, TZDs, like metformin, need the presence of insulin to mediate a blood glucose-lowering generate.
<b>New drug modalities:</b> Incretins (exendin-4, liraglutide, vildagliptin, sitagliptin)	The small intestine secrete glucagon-like peptide-1 (GLP-1) as vigorous as glucose-dependent insulin tropic polypeptide (GIP), These hormones excite insulin secretion, insulin gene expression, pancreatic beta-cell expansion.

## 9 Diabetes care and medication

Diabetes is not completely curable it wants a being time commitment to do what is necessary to manage diabetes. Through proper management it can be controlled to a greater amount. This entire factor is organized. And in the casing of Type-2 diabetes<sup>29</sup>, It can be totally controlled in various cases with diet and exercise. Daily monitoring of blood glucose level through a glucometer.

1. Insulin injections and additional medications to be taken as directed.
2. Organization of diet and weight control.
3. Managing a everyday exercise plan.
4. Daily monitoring and organization of skin and foot think about.
5. Every day oral hygiene.
6. Regular visit to the eye doctor as glowing as the dentist.

7. Regular remedial for blood pressure etc.

## 10 Diabetes know how to be managed with different types of medications

1. Exogenous insulin.
2. Oral hypoglycaemic mediator.
3. Alternative medicines resembling herbal treatment, Yoga, Unani medicines etc<sup>30, 31</sup>.

## 11 Mechanism of Action of Herbal Antidiabetic

1. The ant-diabetic activity of herbs depends upon diversity of mechanisms. The mechanism of action of herbal anti-diabetic may be.
2.  $\alpha$ -amylase inhibition.
3. Inhibition in renal glucose reabsorption.
4. Stimulation of insulin secretion beginning beta cells of islets or/with

5. inhibition of insulin derivative process.
6. Cortisol lowering actions.
7. Insulin resistance reduction. Providing assured necessary fundamentals like calcium, zinc, magnesium, manganese and copper intended for the  $\beta$  -cells.
8. Regenerating and/before repairing pancreatic  $\beta$  cells.
9. Increasing the amount and numeral of cells in the atoll of Langerhans.
10. Stimulation of insulin emission.
11. Stimulation of glycogenesis amid hepatic glycolysis.
12. Inhibition of  $\beta$  -galactocidase among  $\alpha$ -glucocidase.
13. Protective consequence on the destruction of the  $\beta$  cells.
14. Improvement in digestion alongside with reduction in blood sugar and urea.
15. Prevention of pathological alteration of starch to glucose<sup>31, 33</sup> (Table 2 and Table 3).

## 12 Conclusion

Herbal therapies used for diabetes have been followed all-over the World effectively. Herbs are used to manage Type I and Type II diabetes and their complications. The potency of herbal drugs is considerable & they include negligible side effects than the synthetic ant-diabetic drugs. So it was concluded to facilitate these herbal formulation is supportive to lower glucose level during treatment of diabetes patients. Thus lots of different plants contain be used individually or in formulations used for treatment of diabetes.

## 13 Conflict of interests

The author declared none

## 14 Author's contributions

TK and PP carried out literature review and draft the manuscript. AR participated in collection of data. All authors read and approved the final manuscript.

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