INTRODUCTION
Prevalence of diabetes

Figure 1

The top 10 countries, in numbers of people with diabetes, are:

<table>
<thead>
<tr>
<th>Country</th>
<th>2000 (millions)</th>
<th>2030 (millions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>India</td>
<td>31.7</td>
<td>79.4</td>
</tr>
<tr>
<td>China</td>
<td>20.8</td>
<td>42.3</td>
</tr>
<tr>
<td>Indonesia</td>
<td>17.7</td>
<td>30.3</td>
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<tr>
<td>Japan</td>
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<tr>
<td>Pakistan</td>
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<tr>
<td>Russia</td>
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<tr>
<td>Brazil</td>
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<tr>
<td>Italy</td>
<td></td>
<td></td>
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<tr>
<td>Bangladesh</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Prevalence of diabetes (%) in persons 35 - 64 years

- < 3
- 3 - 5
- 6 - 8
- > 8

2000 = number of people with diabetes in 2000
2030 = number of people with diabetes in 2030

Source: Wild et al, 2004
1.1 Prevalence of Diabetes Mellitus (Figure - 1)

In the past decades, diabetes mellitus has become a major health problem worldwide, reaching epidemic proportions in many developing countries including India.\(^1\) World wide projections suggest that > 220 million people will have diabetes by the year 2010 and majority of these (approximately 213 million) will have type – II diabetes.\(^2\) Diabetes mellitus has emerged as a leading metabolic disorder, affecting more than 350 million individuals as of 2007. India is the diabetic capital of the world, with 41 million people affected with the disease.\(^3\)

It is the most prevalent disease in the world affecting 25% of population and afflicts 150 million people and may raise to 300 million by 2025. Diabetes mellitus is considered as one of the five leading cause of death in the world. India with largest diabetic population is expected to have 57.2 million diabetic patients by the year 2025.\(^4\) The National Urban Diabetes study (NUDS) was recently conducted in six major cities covering all regions of the country. In each of the cities studied, prevalence of diabetes is higher than 9% ranging from 9.3% - 16.6%. The average diabetic prevalence in urban Indian adults is 12.1%. Prevalence of diabetes in rural area is 4 to 6 times lower than in the cities.\(^5\)

Recently WHO and International Diabetic Federation (IDF) reports show that the incidence of diabetes is increasing at an epidemic rate, especially in developing countries, probably due to rapidly changing life style, eating habits and environmental conditions.\(^6\) India has been projected by WHO as the country with fastest growing population of diabetic patients. It is estimated that between 1995 – 2025 diabetic patients in India will increase by 195%. 

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* A Study On Antidiabetic Potentials Of Selected Herbs And A Herbal Formulation
1.2 Definitions of Diabetes mellitus

Diabetes mellitus is considered as a complex multisystemic disorder characterized by a relative or absolute insufficiency of insulin secretion or concomitant resistance of the metabolic action of insulin on target tissues. Diabetes mellitus is a chronic disease characterized by derangement in carbohydrate, fat and protein metabolism. It is well established that diabetes mellitus is a condition with a range of abnormalities rather than a single disease. There are number of symptomatic abnormalities in various tissues that characterized diabetes. The clinical importance of diabetes lies mainly in its propensity to produce macrovascular and microvascular complications leading to cardiovascular diseases, cerebrovascular diseases, retinopathy, nephropathy and foot problems, which account for considerable morbidity and mortality throughout the world.³

A predisposition to the disease is probably inherited as an autosomal recessive trait. About 25% of relatives of diabetic patients show abnormal glucose tolerance curves compared to 1% in the general population.

Development of diabetes mellitus involves several pathogenic processes. These include processes, which destroy the beta cells of the pancreas with consequent insulin deficiency. Outcome of insensitivity or lack of insulin deficiency that results in the deficient action of insulin on target tissue leading to the abnormalities of carbohydrate, fat and protein metabolism. Diabetic patients have accumulation of sugar, and its appearance in the blood (hyperglycemia) and then in urine (glycosuria).⁷

1.3 Classifications of Diabetes mellitus

Diabetes mellitus is classified on the basis of the pathogenic process that leads to hyperglycemia.
Etiologic classification of diabetes mellitus

1.3.1 Type - I Insulin Dependent diabetes mellitus (IDDM) or Juvenile onset diabetes mellitus.

In IDDM, there is β - cell destruction in pancreatic islets, leading to absolute insulin deficiency. It affects approximately 5 – 10 % of people with diabetes. There are two forms of type – I diabetes.

Type – I A: This is an immune mediated diabetes mellitus, where autoantibodies cause beta cell destruction and are detectable in blood.

Type – I B: This is an idiopathic diabetes mellitus, where β – cell antibody is not found. It is a rare form of the disease with no known cause.8

In all cases of type – I diabetes, the insulin levels are low or very low, and patients are prone to ketosis. This type of diabetes mellitus is less common and has a low degree of genetic predisposition.

1.3.2 Type - II Non Insulin Dependent diabetes mellitus (NIDDM) or Maturity onset diabetes mellitus.

Type – II diabetes mellitus is a heterogenous group of disorder characterized by variable degrees of insulin resistance, impaired insulin secretion and increased glucose production. NIDDM has a high degree of genetic predisposition and generally has a late onset.9 The most common form of diabetes is type – II diabetes. About 90 – 95 % of people with diabetes have type – II. This form of diabetes is most often associated with old age, obesity, family history, previous history of gestational diabetes and physical inactivity. About 80% of people with type – II diabetes are overweight.
1:3:3  Gestational Diabetes mellitus (GDM)

Gestational diabetes mellitus is defined as diabetes that has its initial onset during pregnancy and resolves after the end of the pregnancy. Women who have GDM have 20–50% chance of developing type – II diabetes within 5–10 years.10

1.3.4  Other specific types

1.3.4.1 Genetic defects of beta – cell function: This form of diabetes formerly referred to as Maturity Onset Diabetes of Young (MODY). It has impaired insulin secretion with minimal or no defect in insulin.

1.3.4.2 Genetic defects in insulin action: Most genetic defects in insulin action involve the insulin receptor. Other defects may be in insulin receptor proteins or in the PPAR – gamma receptor or in both.11

1.3.4.3 Disease of the exocrine pancreas: Any process that diffusely injures the pancreas causes diabetes such as pancreatitis, trauma, infection, pancreatic carcinoma and pancreatectomy.

1.3.4.4 Endocrinopathies: Several hormones such as Growth hormone, cortisol, glucogons, and epinephrine may antagonize insulin action. Diseases associated with excess secretion of these hormones can cause diabetes.12

1.3.4.5 Drug or chemical induced diabetes: Many drugs can impair insulin secretion, these drugs may not by themselves, cause diabetes but they may precipitate diabetes in person with insulin resistance.13,14

1.3.4.6 Diabetes due to Infections: Certain virus has been associated with β cell destruction which may leads to type – I diabetes.
1.3.4.7 Uncommon forms of immune – mediated diabetes: Type – I diabetes is caused by an autoimmune attack of the pancreatic islets. Immune – mediated attacks are also responsible for rarer symptoms which include ‘Stiff Man syndrome’ and anti – insulin antibody mediated hyperglycemia.

1.3.4.8 Other genetic Syndromes: Down syndrome, Diabetes Insipidus, Diabetes Mellitus, Optic Atrophy, and Deafness (DIDMOAD) and myotonic dystrophy may also cause diabetes.\(^{15}\)

1.4 Symptoms of Diabetes mellitus:

The two types (I and II) of diabetes have very similar symptoms. The first symptoms are related to the direct effects of high blood sugar levels. When the blood sugar level rises above 160 to 180 mg/ dl, sugar spells into the urine. Symptoms may develop quite rapidly in type – I diabetes, particularly in children. In type – II diabetes, it develops slowly and may not have any symptoms for year or decades, before they are diagnosed.

The most common symptoms of diabetes are polyuria, polyphagia, polydypsia and weight loss. Apart from these symptoms, patients have blurred vision, burning sensation during urination, burning sensation in the hands and in the soles of the feet. Cuts, bruises, sores and irritations suffered by the diabetic do not heal properly and susceptible to infections.\(^9\) (Figure 2)

1.4.1 Symptoms of type – I Diabetes mellitus:

The symptoms of type – I diabetes can develop suddenly. The most common symptoms include:

High level of blood and urine, unusual thirst, frequent urination, extreme hunger but loss of weight, blurred vision, nausea and vomiting, extreme weakness and tiredness, irritability and ketoacidosis.
1.4.2 Symptoms of type – II Diabetes mellitus:

Type – II diabetes mellitus usually occurs above the age of 30. Obesity is one of the major risk factor for type – II diabetes and 80% - 90% of people with diabetes are due to this factor. The common symptoms of type – II diabetes mellitus are:

- Extreme fatigue
- Polyuria
- Polydypsia
- Polyphagia
- Poor wound healing
- Infections and
- Altered mental status.
1.5 Complications of Diabetes mellitus:

Diabetes is susceptible to two major metabolic complication viz., acute complication and chronic complication

1.5.1 Acute complications:

1.5.1.1 Diabetic ketoacidosis (DKA): (Figure 3)

DKA results due to relative or absolute insulin deficiency combined with excessive counter regulatory hormones like glucagon, catecholamines, cortisol and growth hormone. Lack of insulin causes the liver to convert fat into ketone bodies, a fuel mainly used by the brain. Elevated levels of ketone bodies in the blood decrease the blood’s pH leading to the symptoms of DKA. Physical findings include poor skin turgor, kussmaul respiration, hypotension, shock and coma.

1.5.1.2 Nonketotic hyperosmolar coma (NKHC):

NKHC is a type of diabetic coma associated with a high mortality that is seen in diabetes mellitus type II. Nonketotic coma is precipitated by an acute illness, myocardial infarction or stroke.17
SCHEMATIC DEPICTION OF THE DEVELOPMENT OF DIABETIC KETOACIDOSIS DUE TO LACK OF INSULIN

Symptoms produced are shown within boxes

- Insulin Lack
- Ketosis
- Hyperglycaemia
- Acidosis
- Glycosuria
- Ketosis
- Osmoticdiuresis
- Loss of electrolytes ($Na^+, K^+, Ca^{2+}, Mn^{2+}$)
- Intracellular K+ depletion
- Hypertension
- Shock
- Tachycardia
- Impairment of glucose entry into Brain
- Impairment of fixed Cations in urine
- Hyperventilation
- Loss of $H_2O$
- Dehydration
- Hyperosmolarity of blood
- Intracellular Dehydration
- Impairment of Consciousness

Figure 3

A Study On Antidiabetic Potentials Of Selected Herbs And A Herbal Formulation
1.5.2 Chronic complications: (Figure – 4)

The chronic complications of diabetes mellitus affect many organ systems and are responsible for the majority of morbidity and mortality associated with the disease. Chronic complications can be divided into vascular and nonvascular complications. The vascular complications of diabetes mellitus are further subdivided into microvascular (retinopathy, neuropathy, nephropathy) and macrovascular complications (coronary artery disease, peripheral arterial disease, cerebrovascular disease). Nonvascular complications include problems such as gastroparesis, infections and skin changes.

1.5.2.1 Microvascular complications:

Diabetic retinopathy:

Diabetic retinopathy (damage to the retina) is caused by complications of diabetes mellitus, which could eventually lead to blindness. It is an ocular manifestation of systemic disease, which affects up to 80% of all diabetics who have had diabetes for 15 years or more. Diabetic retinopathy is a result of microvascular retinal changes. Hyperglycemia-induced pericyte death and thickening of the basement membrane lead to incompetence of the vascular walls.\textsuperscript{18}

Diabetic neuropathy:

Diabetic neuropathy occurs in approximately 50% of individuals with long-standing type 1 and type 2 diabetes mellitus. It may manifest as

(i) Polyneuropathy: Most frequently symptoms include distal sensory loss, hyperesthesia, paresthesia, and dysesthesia, sensation of numbness, tingling, sharpness, or burning that begins in the feet and spreads proximally.

(ii) Mononeuropathy: It is less common than polyneuropathy in diabetes mellitus and presents with pain and motor weakness in the distribution of a single nerve.
Complications and Symptoms of Diabetes:

- Stroke (brain injury)
- Eye disease, blurred vision
- Increased thirst
- Nerve damage, peripheral neuropathy
- Kidney disease
- Weight loss
- Impaired bloodflow to the lower extremities
- Increased urination
- Heart disease, high blood pressure, increased fatigue
(iii) Autonomic neuropathy: Diabetes mellitus-related autonomic neuropathy may involve multiple systems, including cardiovascular, gastrointestinal, genitourinary sudomotor and metabolic systems. Autonomic neuropathies affecting the cardiovascular system cause a resting tachycardia and orthostatic hypotension.

As with other complications of diabetes mellitus, the development of neuropathy correlates with the duration of diabetes and glycemic control; both myelinated and unmyelinated nerve fibers are lost.

Diabetic nephropathy:
Diabetic nephropathy (Nephropatia diabetica), is due to longstanding diabetes mellitus, and is a prime cause for dialysis in many western countries. Diabetic nephropathy is the most common cause of chronic kidney failure and end-stage kidney disease.19

1.5.2.2 Macrovascular complication:

Cardiovascular disease:
It refers to class of diseases that involves the heart or blood vessels (arteries and veins). Lipid, like cholesterol, cholesterol ester, lipoprotein such as LDL, VLDL are deposited on the inner surface of artery.

Heart disease and strokes:
Patients with diabetes are 2-4 times more likely to have heart disease and more likely to suffer stroke. This is observed in 75 percent of diabetes-related death. Diabetes also accelerates the hardening of the arteries (atherosclerosis) of the larger blood vessels, leading to coronary heart disease (angina or heart attack), stroke and pain in the lower extremities because of lack of blood supply.20
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Diabetic foot:

Due to arterial abnormalities and diabetic neuropathy as well as a tendency to delayed wound healing; infection or gangrene of the foot is relatively common in diabetic patients. Gangrene is the necrosis and subsequent decay of body tissues caused by infection or thrombosis. It is usually the result of critically insufficient blood supply (peripheral vascular disease), by external injury and subsequent contamination with bacteria.

1.5.2.3 Nonvascular disease:

Certain types of infection, such as bacteriuria, occur more frequently in diabetic patients than in non-diabetic matched control. There are also several unusual infections that occur almost exclusively in diabetics. Diabetic dermopathy is characterized by atrophic brown spots on the skin, usually in the pretibial area (Shin spots). These changes may be a consequence of increased glycosylation of tissue proteins or vasculopathy. Eruptive xanthomas may develop in some poorly controlled diabetic, hypertriglyceridermia.21

1.6 Antidiabetic Drugs

Allopathic therapeutic interventions available for diabetes mellitus which are used to stabilize blood sugar level and eliminate the symptoms of high blood sugar. The antidiabetic drugs available are insulin, sulfonylurea, biguanides, alphaglucosidase inhibitors, meglitinides, Thiazolididine dione, and some sulfonylurea like glyburide, glipizide, chlorpropamide and glimepiride. These drugs stimulate β - cell insulin secretion by binding to sulfonylurea receptor, resulting in cell membrane depolarization, increased intracellular calcium and subsequent release of insulin8. Population rise, inadequate supply of drugs, prohibitive cost of treatments, side effects of several allopathic drugs and development of resistance to currently used drugs for infectious diseases have led to increased emphasis on the use of plant materials as a source of medicines for a wide variety of human ailments including diabetes.
1.7 Traditional Medicines – Sources of New Drugs

Traditional systems of medicines remain the major source of health care for more than two thirds of world’s population and impressive progress has been made in certain developing countries like China and India through integration of traditional with western systems of medicines.

The first mention of traditional medicines is found in Rig-Veda and Yajur Veda both around 2000 BC. Rig – Veda mentions 67 traditional drugs, Yajur – Veda contains 81 and Atharvaveda (1600-1100 BC) includes 290 traditional drugs. Charak Samhita (900 BC) is the first recorded treatise of Ayurveda which describes 341 plants and plant products for use in medicine. In 1550 AD, Bhava Mishra of Magadha in his treatise mentions 470 medicinal plants. In addition there are over 70 Nighantu Granthas, Written between the 7 th and 16 th centuries which provide very valuable information about medicinal plants as curatives for various ailments.

India is known for its biodiversity and has a rich heritage of herbs. A number of medicinal plants are traditionally used for over 1000 years and are included in herbal preparations. WHO has listed 21,000 plants, which are used for medicinal purpose around the world. Among these 2500 species are in India, out of which 150 species are used commercially on a fairly large scale.

In the last few years, there has been an exponential growth in the field of herbal medicine and is gaining popularity both in developing and developed countries because of their natural origin and less side effects. Many traditional medicines that are in use from time immemorial are found to be derived from plants, minerals and organic matter.
Introduction

1.8 Herbs in the Management of Diabetes mellitus

In recent decades there have seen a resurgent interest in traditional plant treatments for diabetes. This has pervaded nutrition, the pharmaceutical industry and academic research, fuelled by a growing public interest and awareness of so-called complementary and natural types of medicine. Before the advent of insulin therapy in 1922, starvation diets and traditional plant treatments were the cornerstone of antidiabetic therapies. Traditional herbal preparations continue to form the predominant therapeutic approach in many deprived regions of the world.\textsuperscript{25}

Ethno botanical studies on traditional herbal remedies used in diabetes around the world have identified more than 1200 species of plants with hypoglycemic activity. These plants are broadly distributed throughout 725 different genera. The pharmacopoeia of India is especially rich in herbal treatments for diabetes. Eighty-five percent of the antidiabetic plants used most widely all around the world are prescribed in India.\textsuperscript{26}

In view of wide usage of plant drug in diabetes mellitus, WHO expert committee on diabetes (1980) has recently recommended that the need of the hour is to validate scientifically the effect of antidiabetic agents of plant origin used in traditional medicines.\textsuperscript{11} Today more than 200 traditional medicinal plants are in use in the management of diabetes mellitus and are widely practiced in South India. Plant sources are used as single drug or as a combination of many plant sources as formulation. Common antidiabetic formulations available in the market are Nishamlaki, Diabecon, Coagent db+ and Diasulin which comprises of many common plant sources.

Ayurvedic herbal drugs for diabetes mellitus are based on the principles of *rasa* (taste), *guna* (physiochemical properties), *veerya* (potency), *vipaka* (post digestive effect), and *prabhava* (unique action). Each of these principles are felt to have specific effect on the doashas and functions of the body, which are utilized for antidiabetic and other therapeutic effects.\textsuperscript{27}
Introduction

Despite the great strides that have been made in understanding the management of diabetes, there is an unabated increase in the disease and disease related complications. In spite of the known antidiabetic medicines in pharmaceutical market, remedies from medicinal plants are used with success.\textsuperscript{14}

There is an increasing demand among patients to use the natural products with antidiabetic activity so as to avoid the side effect associated with the use of insulin and other proven synthetic hypoglycemic agents. Although insulin is a life – saver it is not a cure. The majority of type 2 patients are sufficiently insulin resistant and for these patients insulin is not necessarily the ideal treatment strategy. Both type 1 and type 2 diabetes carries an appalling burden of chronic macrovascular, retinal, renal and neuropathic complications. These complications are associated with the extent and duration of hyperglycemia. Glycemic control also defers with the onset and their progression of diabetes mellitus.

Synthetic oral hypoglycemic agents and insulin can produce a series of side effects including hematological, gastro – intestinal reactions, hypoglycemic coma and disturbances in liver and kidney metabolism and they may not be ideal for use during pregnancy.\textsuperscript{20} Hence there is an urgent need to develop an agent to combat hyperglycemia and its accompanying complications. As indigenous herbs are gaining momentum in past few decades and due to its vast chemical diversity, and less side effects they can be restored for developing a safe efficacious, cost effective antidiabetic drug.

Hence the present dissertation aims at developing a scientifically validated antidiabetic herbal formulation from traditional drug sources.