1.1. Present status of Diabetes mellitus and treatment options in India

Diabetes represents a spectrum of metabolic disorders, which has become a major health challenge worldwide (King et al., 1998). The unprecedented economic development and rapid urbanization in Asian countries, particularly in India has led to a shift in health problems from communicable to non-communicable diseases. Of all the non-communicable diseases, diabetes and cardiovascular diseases lead the list.

Diabetes is pandemic in both developed and developing countries. In 2000, there is an estimated 175 million people with diabetes worldwide and by 2030, the projected estimate of diabetes is 354 million (Wild et al., 2004). The greatest relative rise is predicted in the developing countries of the Middle Eastern Crescent, Subsaharan Africa and the Indian subcontinent. By the year 2030, over 85 percent of the world’s diabetic patients will be in developing countries. In India alone, the prevalence of diabetes is expected to increase from 31.7 million in 2000 to 79.4 million in 2030 (Wild et al., 2004).

India leads the world with largest number of diabetic subjects earning the dubious distinction of being termed the “Diabetes capital of the world”. According to World Health Organization (WHO) reports, 32 million people had diabetes in the year 2000. International Diabetes Federation, (2006) published the number of people with diabetes in India currently is around 40.9 million and is expected to rise to 69.9 million by 2025 unless urgent preventive steps are taken.
Fig. 1.1. Estimated Number of Diabetic subjects in India:

Fig. 1.2. Recent population based studies showing the prevalence of type 2 diabetes in different parts of India:
A National survey of diabetes conducted in six major cities in India in the year 2010 has shown that the prevalence of diabetes in urban Indian adults was 12.1%. The onset of diabetes among Indians is about a decade earlier than their western counterparts and this has been noted in Asian Indians in several studies (Ramachandran et al., 1992 and 2001).

In the National survey 54.1% of diabetes developed it in the most productive years of their lives i.e. before the age of 50 years and they also had a higher risk of developing chronic complications of diabetes (Ramaiya et al., 1990, Ramachandran et al., 1992 and 2001) The prevalence of Type 2 diabetes is 4-6 times higher in the urban areas as compared to rural areas.

The prevalence of impaired glucose tolerance (IGT) in the rural population is also high at 7-8%, which indicates presence of a genetic basis for Type 2 diabetes in ethnic Indian population (Viswanathan et al., 1996, Debra., 1991., Debra., et al 1991).

On the basis of etiology two main categories of diabetes are recognized, viz. Primary diabetes and Secondary diabetes

1. **Primary diabetes**

   Juvenile onset diabetes which is also referred as Type 1 or Insulin dependent Diabetes mellitus (IDDM). In Juvenile onset diabetes there is a profound decrease in the number of beta cells in the islet of Langerhans and thus there is absolute deficiency of insulin. The main treatment for this type is insulin. Maturity onset diabetes which is also referred as Type II /Non-insulin dependent Diabetes mellitus (NIDDM). The patients are usually obese and the treatment is usually dietary, though supplementary oral hypoglycaemic drugs. It is diagnosed by blood or urinary glucose
measurement. Insulin resistances as well as loss of insulin secretion contribute to the onset of disease.

2. Secondary diabetes

The symptoms result from the following pancreatic dysfunction (pancreatitits, pancreatectomy). Hormonal imbalance (eg, Acromegaly, pheochromacytoma, pheochromacytoma, Cushing’s syndrome, glucagonoma). Drugs or chemical induced reactions (eg: glucocorticoids, anticancer agents, streptozotocin or diazoxide, thiazide, some psychoactive agents).

In moderately severe early diabetes, following features are present. Hyperglycemia, Glycosuria, Loss of weight due to increased breakdown of fat and tissue protein. Increased production of ketone bodies by liver and their incomplete utilization by the tissue leading to their accumulation in blood (Ketosis) and elimination in urine (Ketonuria). Lowering of pH of blood due to circulating keto acids (acidosis). Dehydration due to elimination of large amounts of water with glucose in urine. Increased levels of lipid, fatty acids and cholesterol in blood. Increased tendency to develop cataract in the eye and atheromatous and artherosclerotic lesions of blood vessels (Macleod et al., 1997).

1.2. Synthetic Drugs and the Treatment of Diabetes mellitus

The major treatment options are insulin, Oral hypoglycaemic Drugs, Herbal Drugs.

Insulin

Insulin is hormone secreted by the β cells of the islets of langerhans in the pancreas. The diabetic mellitus has been well known as a wasting disease due to insulin deficiency in human beings. The pancreas secretes insulin. Carbohydrate
metabolism is primarily under the control of insulin. Insulin deficiency occurs in a person due to the functional disorder of the pancreas.

**Oral Hypoglycaemic Drugs**

These drugs lower blood glucose level and are effective orally. Some of the available antidiabetic drugs are.

(1) Sulfonylureas

Tolbutamide, Glibenclamide, Chlorpropamide Glipizide, Acetohexamide Gliclazide, Tolazamide.

(2) Biguanides

Phenformin, Metformin.

(3) Thiazolidinediones

Rosiglitazone, Pioglitazone, Troglitazone.

**Regular antidiabetic drugs:**

The following table compares some common anti-diabetic agents, generalizing classes although there may be substantial variation in individual drugs of each class. Most anti-diabetic agents are contraindicated in pregnancy, in which insulin is preferred (Agabegi et al., 2008).

<table>
<thead>
<tr>
<th>Agent</th>
<th>Mechanism</th>
<th>Site of action</th>
<th>Main advantages</th>
<th>Main side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfonylureas</td>
<td>Stimulating pancrease to increase insulin production</td>
<td>Pancreas</td>
<td>Effective Inexpensive</td>
<td>Hypoglycemia Weight gain</td>
</tr>
<tr>
<td>Metformin</td>
<td>Decreases</td>
<td>Liver</td>
<td>May result in GI symptoms</td>
<td></td>
</tr>
</tbody>
</table>
1.3. **Herbal Drugs and Treatment of Diabetes mellitus**

Since from ancient times a number of herbal medicines have been used in the treatment of Diabetes mellitus. There is increasing demand by patients to use the natural products with antidiabetic activity. Herbal medicines for diabetes can be classified into four categories according to their mode of action (Wadkar et al., 2008).

- Drugs acting like insulin.
- Drugs acting on insulin secreting beta cells.
- Drugs acting by modifying glucose utilization.
- Drugs acting by miscellaneous mechanisms.

**Herbal drugs acting like insulin**

*a) Momordica charantia*

Fruits of *Momordica charantia* have been successfully used by diabetic patients and their crude extract has been shown to possess hypoglycaemic activity. Khanna and jain isolated a hypoglycaemic peptide (polypeptide-P) from seeds and

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<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acarbose</td>
<td>Reduces intestinal glucose absorption</td>
<td>GI tract</td>
<td>Low risk, including diarrhea, abdominal cramping, flatulence</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>Reduce insulin resistance</td>
<td>Fat, muscle</td>
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other tissues of *Momordica charantia*. They reported that polypeptide is a very effective hypoglycaemic agent when administered subcutaneously to langurs and humans. Singh et al. have reported hypoglycaemic effect of acetone extract of whole fruit powder of *Momordica charantia*.

(II) **Drugs acting on insulin secreting β cells**

a) *Allium cepa*

*Allium cepa* (onion) was investigated for its hypoglycaemic activity by Collip and Janet. Laurin, Brahmachari and Augusti reported that the petroleum ether extract of dried onion has hypoglycaemic activity and suggested that it can be a useful substitute for tolbutamide in controlling alloxan diabetes in rats.

b) *Pterocarpus marsupium*

Rajasekharan and Tuli carried out clinical trials and found that Pterocarpus marsupium bark is effective in Type 1 *Diabetes mellitus*. Later Charkravarthy *et al.*, reported epicatechin to be the active hypoglycaemic constituent.

c) *Aloes*

Ghannam *et al.* carried out their study on 5 patients with NIDDM and also on alloxan treated diabetic mice. They reported that oral administration of aloes lowers the fasting serum glucose levels in normal and diabetic subjects.

(III) **Plant drugs acting by modifying glucose utilization**

*Zingiber officinale* (ginger), *Cyamospsis tetragonolobus* (Gowar plant) and *Grewia asiatica* are reported to produce hypoglycaemia by modifying glucose utilisation. Sharma and Shukla reported that ginger juice has glucose lowering effect in normal fasting animals and in alloxan diabetic animals. Jenkins *et al.* reported that the hypoglycaemic effect of *Cyamospsis tetragonolobus* in diabetic and normal subjects. Gowar plant and its seeds at a dose of 40 g/kg showed hypoglycaemic
activity similar to that of tolbutamide. The mechanism of action of gowar is probably related to its ability to increase the viscosity of gastrointestinal contents, slow gastric emptying and also act as a barrier to diffusion. The workers concluded that gowar produces its hypoglycaemic action by acting at an extrapancreatic site. The aqueous extract of Grewia asitica was tested in diabetic cats and rabbits of both sexes by Pakrashi and Mukherjee. These workers reported that the fasting blood sugar levels come down to normal after the treatment and remain as such after discontinuation of treatment for another 15 days.

(IV) Drugs acting by miscellaneous mechanisms

a) Leguminous plants

Hypoglycemic activity of some leguminous plants was studied by Singh et al. and reported that legumes in diet could reduce glucose levels in normal rats than could a normal diet. Chopra (1955) reported that leguminous plants in diet could reduce blood sugar levels and cholesterol levels because of their dietary fiber content.

b) Euphorbia prostrata and Fumaria parvia parviflora

Aktar et al., reported extracts from these plants reduce blood sugar levels in normal rabbits but not in diabetic rabbits.

A few other plants with hypoglycaemic activity are Panax ginseng, Dioscorea dumatorum, Cuminum nigrum, Ocimum sanctum, Curcuma longa, Phyllanthus embelica (Hakim 1995).

1.4. Status of medicinal plants in the treatment of diabetes in the traditional system

Ayurveda and other Indian literature advocate the use of medicinal plants in treatment of various human diseases. India has about 45,000 plant species and among them, several thousands have been claimed to possess medicinal properties. Among
them, 30 plants and their products (active natural principles and crude extracts) that have been mentioned used in the Indian traditional system of medicine have shown experimental or clinical antidiabetic activity. *Trigonella foenumgraecum, Momordica charantia, Tinospora cordifolia, Enicostema littorae, Gymnema sylvestre, Azadirachta indica, Syzigium cumini* are some of the most effective and the most commonly studied Indian plants in relation to diabetes. Herbal medicines are often used as therapeutic remedies in combination with allopathic drugs (Ramesh et al., 2003., Babara et al., 1993) Usually ayurvedic drugs are being used due to their minimum toxicity (Yadav and Vats 2002). The basis prescription of ayurvedic drugs was mainly found to be past experience of the patients. Practicing physicians expected that controlled clinical trials of the herbal antidiabetic should be conducted in humans at different hospitals to substantiate the efficacy claim. Ginger, jamun, karela, methi are being used as home remedies in *Diabetes mellitus* due to their proved antihyperglycemic activity (Kar et al., 2003).

Literature revealed that while evaluating comparative hypoglycemic activity of the experimental herbal samples, significant blood glucose lowering activities are observed in decreased order in the following herbal samples: *Coccinica indica, Tragia involucrate, G. sylvestre, Pterocarpus marsupium, T. foenumgraecum, Moringa oleifera, Eugenia jambolana, Tinospora cordifolia, Swertia chirayita, Momordica charantia, Ficus glomerata, Ficus benghalensis, Vinca rosea, Premna integrifolia, Mucuna prurita, Terminalia bellerica, Sesbenia aegyptiaca, Azadirachta indica, Dendrocalamus hamiltonii, Aingiber officianle, Aegle marmelos, Cinnamomum tamala, Trichosanthes cucumerina and Ocium sanctum* (Kar et al., 2003., Chattopadhyay, 1999).
**Some minerals used in Diabetes mellitus**

Some of the mineral remedies consist of Bangabhasma (calcinated tin), Jistbhasma (calcinated zinc), Abrhabhasma (mica ash), and Lohabhasma (calcinated iron). Some of the commercial preparations (e.g., Nowojar) containing above bhasmas were very effective in NIDDM; in case of IDDM, it helped in reducing dose of insulin. Some complexes with metformin and tolbutamide with zinc, cadmium, cobalt and copper have some complexes with the exception of complexes have shown good hypoglycemic effect. Zinc complexes have shown to have good blood-sugar-lowering activity. Shilajit, an organo-mineral preparation found in nature, has been used as a tonic in *Diabetes mellitus*.

**Rasayana therapy in Diabetes mellitus**

Rasayana is an important branch of Ayurveda. The main goal of Rasayana therapy is better quality of life with increased lifespan (Lebovitz, 1999). Rasayana includes drug formulations, dietary regime and code of conduct. Many of the drugs used in Rasayana therapy in *Diabetes mellitus* have excellent antioxidant properties, like Phyllanthus emblica, Azadirachta indica, Ocium sanctum and Tinospora cordifolia. The Rasayana approach to treat diabetes consists of Aeara Rasayana (antistress), Ajasrika Rasayana (dietary control), Osad Rasayana (antistress), Kamya Rasayana (preventive), Naimittika (Varier, 1995., Cragg, 1997., Bensky and Gamble 1996).

**1.5. The objectives of the Proposed Study**

The plants provide a potential source of hypoglycemic drugs because many plants and plant derived compounds have been used in the treatment of diabetes. Hence, they play an important role as alternative medicine due to less side effects and low cost. The synthetic hypoglycemic agents can produce serious side effects
including hematological effects, coma and disturbances of the liver and kidney. In addition, they are not suitable for use during pregnancy (Larnner et al., 1985., Momin et al., 1987). Hence, scientifically validated and technologically standardized herbal medicines may be derived using a safe path of reverse pharmacology approach based on traditional knowledge database. Development of anti-diabetic drugs from plants is one of the fast approaches to new drug development with 20% success rate. District of Tumkur is a hub of Viadyas, who practice traditional medicine especially available in Siddrabetta, a protected medicinal plant forest. These traditional Viadyas uses various herbs for the treatment of diabetes and its complications. In this connection, the author has interacted with several Viadyas, Pandith Shiva Shankar, President, Paramparika Viadyas association, Tumkur, and Pandith Paramashivaiah, Nadi viadya, Gowdana katte, Tumkur. Based on several interactions, the author has undertaken the present study to provide a scientific proof to the traditionally used herbs. In addition, the novelty of the present study involves scientific evaluation of plants with traditionally claimed in the treatment of diabetes by communication with several Viadyas of Siddarabetta region.
Proposed study

1. Survey of anti diabetic herbs used by traditional Viadyas of Siddrabetta region, Tumkur district, Karnataka.
2. Collection, authentication and preparation of voucher specimens of the above selected plant material.
3. Preparation of alcoholic and aqueous extracts of the above selected herbs.
4. Screening of the selected extracts for antioxidant evaluation by using DPPH, ABTS, Nitric oxide scavenging and H2O2 assays.
5. Anti-diabetic evaluation of all the extracts using in vitro α-amalyse and α-glucosidase enzyme inhibition assays.
6. In Vivo anti-diabetic evaluation of all the extracts by using normoglycemic rats.
8. Preliminary phytochemical analysis to know the chemical profile of more effective antidiabetic plants
9. Chemopprofile study of active extracts to identify bioactive compounds using HPTLC.

Plants selected for the proposed study.

1. Madhuca indica (fam: Sapotaceae)
2. Anacardium occidentale L. (fam: Anacardiaceae)
3. Basella alba (fam: Basellaceae)
4. Echinops echinatus (fam: Asteraceae)
5. Holoptelea integrifolia (fam: Ulmaceae)
6. *Caesalpinia bonduc* (fam: Fabaceae)

7. *Limonia acidissima* (fam :Rutaceae)

8. *Bauhinia variegata* L. (fam: Fabaceae)


10. *Ichnocarpus frutescens* (fam: Apocynaceae)

11. *Cressa. cretica* L. (fam: Convolvulaceae)

12. *Amaranthus viridis* L. (fam: Amaranthaceae)


15. *Spondias mangifera* Willd (fam: Anacardiaceae)