2.1 Herbal therapy and diabetes

As per ancient literature, more than 800 plants are reported to have antidiabetic properties (Eddouks et al. 2004). Ethnopharmacological surveys indicate that more than 1200 plants are used in traditional medicine for their alleged hypoglycemic activity (Kesari et al. 2007). Medicinal plants, since times immemorial, have been used in virtually all cultures as a source of medicine. A study of ancient literature indicates that diabetes was fairly well known and well conceived as an entity in ancient India. The knowledge of the system of diabetes mellitus, as the history reveals, existed with the Indians since prehistoric age. Its earliest reference (1000 BC in the Ayurvedic literature) is found in mythological form where it is said to have originated by eating Havisha, (Latha & Pari, 2003) a special food, which used to be offered at the times of yagna organized by Dakshaprajapati. Ayurvedic antidiabetic herbs improve digestive power, increase one of the Rasas (gastric secretions); being Laghu, get easily digested in the body; and being Ruksha, decrease output of overall body fluids e.g. urine, sweat etc. Food items, which are ‘Madhumehaghna’ (antidote), are an important underlying principle of therapy for the prameha (diabetes) patient. Food items which correct the metabolic imbalance by their action e.g. foods exhibiting ‘rasa’, ‘katu’, ‘laghu’, ‘medaghna’, properties are old cereals, roasted cereals, barley, jawar, ragi, mung dal, horsegram, tur dal, drumstick leaves, bittergourd, jamun, amla, fig, raw papaya, milk, meat of animals that live in dry region, etc. The indigenous diet may not be useful in lowering the blood sugar to the same extent as insulin and other hypoglycaemic agents do. But it has some other influences, which may be useful for the management of the disease and its complications (Subbulakshmi & Naik 2001). Indian materia medica has mentioned numerous dravyas, which have been reported effective in ‘Madhumeha’ (Sabu & Subburaju 2002).

Plants-based products have been popular all over the world for the centuries. In diabetes, some herbal alternatives are proven to provide symptomatic relief and assist in the prevention of the secondary complications of the disease. Some herbs have also been proven to help in the regeneration of β-cells and in overcoming resistance. In addition to maintaining normal blood sugar level, some herbs are also reported to possess antioxidant activity and cholesterol-lowering action. The management of type 2 diabetes mellitus (NIDDM) is possible with the drugs that can lower the blood sugar level in one hand and restore the liver glycogen level on the other. In modern system of medicine, there is no drug, which is reported to possess both of these properties (Shrabana et al. 2003). However, the hypoglycemic effect of some herbal extracts have been confirmed in human and animal
models of type 2 diabetes and conventional drugs have been derived from the active molecules of these medicinal plants. Metformin, a less toxic biguanides and potent oral glucose-lowering agent, was developed from *Galega officianalis* and used to treat diabetes (Daniel & Norman, 2001). Out of dozens of oral medications for diabetes, only one medication (metformin) is approved for use in children and it has been originated from herbs (Michael et al. 2005).

Regardless of the type of diabetes, patients are required to control their blood glucose with medications and/or by adhering to an exercise program and a dietary plan. Insulin therapy by injection is given to those with type 1 DM and also to some patients with type 2 DM when oral hypoglycaemic drugs fail to lower blood glucose (Alam & Mahpara 2003). Due to modernization of lifestyle, non-insulin dependent diabetes mellitus is becoming a major health problem in developing countries. Patients with type 2 DM are usually placed on a restricted diet and are instructed to exercise, the purpose of which primarily is weight control. If diet and exercise fail to control blood glucose at the desired level, oral antidiabetic medication is prescribed (Derek 2001). Oral antidiabetic agents exert their effects by various mechanisms: (1) stimulation of β-cells in the pancreas to produce more insulin (sulfonylureas and meglitinides), (2) increasing the sensitivity of muscles and other tissues to insulin (thiazolidinediones), (3) decreasing gluconeogenesis by the liver (biguanides), and (4) delaying the absorption of carbohydrates from the gastrointestinal tract (α-glucosidase inhibitors). These treatments have their own drawbacks, ranging from the developing of resistance and adverse effects to lack of responsiveness in large segment of patients population.

Sulfonylureas lose effectiveness for 44% of patients within six years. Also, these treatments are associated with side effects or even toxic effects (e.g., thiazolidinediones may cause liver toxicity; sulphonylureas might worsen heart disease, lower the glucose below the normal range and increase the body weight gain; bloating, flatulence, diarrhea and abdominal discomfort and pain are the major complaints with glucosidase inhibitors) (Dey et al. 2002 & Michael et al. 2005). According to literature, two-thirds of medications prescribed for use in children have not been proven safe or effective for this patient population (Michael et al. 2005). Moreover, none of these glucose-lowering agents adequately controls the hyperlipidemia that frequently met with the disease. The limitations of currently-available oral antidiabetic agents either in terms of efficacy/safety coupled with the emergence of the disease into a global epidemic have encouraged a concerted effort to discover drugs that can
manage type 2 diabetes more efficiently (Ranjan & Ramanujam, 2002). Also, with increasing incidence of diabetes mellitus in rural population throughout the world and due to adverse effects of synthetic medicine, there is a clear need for development of indigenous, inexpensive botanical sources for anti-diabetic crude or purified drugs.

2.2. Mechanism of action of herbal antidiabetics

The antidiabetic activity of herbs depends upon variety of mechanisms. The mechanism of action of herbal anti-diabetic could be grouped as-

1. Adrenomimeticism, pancreatic β-cell potassium channel blocking, cAMP (2nd messenger) stimulation (Marles & Farnsworth 1996)
2. Inhibition in renal glucose reabsorption (Eddouks et al. 2002)
3. Stimulation of insulin secretion from β-cells of islets or/and inhibition of insulin degradative processes (Pulok et al. 2006)
4. Reduction in insulin resistance (Pulok et al. 2006)
5. Providing certain necessary elements like calcium, zinc, magnesium, manganese and copper for the β-cells (Mohamed et al. 2006)
6. Regenerating and/or repairing pancreatic β-cells (Mohamed et al. 2006)
7. Increasing the size and number of cells in the islets of Langerhans (Mohamed et al. 2006)
8. Stimulation of insulin secretion (Esmaeili & Yazdanparast 2004)
9. Stimulation of glycogenesis and hepatic glycolysis (Miura et al. 2001)
10. Protective effect on the destruction of the β-cells (Kim et al. 2003)
11. Improvement in digestion along with reduction in blood sugar and urea (Krishnan 1968)
12. Prevention of pathological conversion of starch to glucose (Sepha & Bose 1956)
13. Inhibition of β-galactocidase and α–glucocidase (Sharma & Mujumdar 1990)
14. Cortisol lowering activities (Gholap & Kar 2004)
15. Inhibition of α-amylase (Heidari et al. 2005)
16. Preventing oxidative stress that is possibly involved in pancreatic β-cell dysfunction found in diabetes (Hideaki et al. 2005)

Hence, the wide range of plant constituents could have different sites of action within the body, herbs exerts different mechanism of actions including the mechanism of actions of synthetic oral hypoglycaemic drugs.

*Tamarindus* is a monotypic genus and belongs to the subfamily Caesalpinioideae of the family Leguminosae (Fabaceae). *Tamarindus indica* L. commonly known as Tamarind tree is
one of the most important multipurpose tropical fruit tree species in the Indian subcontinent. Tamarind fruit was at first thought to be produced by an Indian palm, as the name Tamarind comes from a Persian word "Tamar-I-hind," meaning date of India. Its name "Amlika" in Sanskrit indicates its ancient presence in the country. *T. indica* is used as traditional medicine in India, Africa, Pakistan, Bangladesh, Nigeria and most of the tropical countries. It is used traditionally in abdominal pain, diarrhea and dysentery, helminthes infections, wound healing, malaria and fever, constipation, inflammation, cell cytotoxicity, gonorrhea, and eye diseases. It has numerous chemical values and is rich in phytochemicals, and hence the plant is reported to possess numerous pharmacological properties like antidiabetic, antimicrobial, antivenomic, antioxidant, antimalarial, hepatoprotective, antiasthmatic, laxative, and anti-hyperlipidemic activity (Farnsworth, 1993). It was mentioned in the Indian Brahmasamhita Scriptures between 1200 and 200 BC. About 370-287 BC, Theophrastus wrote on plants and two descriptions refer to Tamarind, his sources were probably from East Africa (Sofowora, 1993).

### 2.3. Taxonomical Classification

<table>
<thead>
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</tr>
<tr>
<td>Species:</td>
<td><em>indica</em></td>
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</table>
Fig. 10. *Tamarindus indica* L.
2.4. Tamarind Seed

Tamarind seed comprises the seed coat or testa (20-30%) and the kernel or endosperm (70-75%) (Shankaracharya, 1998). It is commercially available as a food additive for improving the viscosity and texture of processed foods. The name "jellose" has been suggested for the seed polysaccharide as it describes both its jelly forming properties and the carbohydrate character (Rao, 1956). It has been recommended for use as a stabilizer in ice-cream, mayonnaise, cheese, and the seed oil is said to be palatable and of culinary quality. The oil is used for making varnish to paint idols and light lamps (Salim, 1998).

2.5. Vernacular names

In India, Tamarind is known by a wide variety of vernacular names: Tetuli (Assamese); Aml, Nuli, Textili Tentul (Bengali); Amali, Ambali (Gujarati); Ambli, Aml, Imli, (Hindi); Puli (Malayalam); Amli, Chinch, Chitz (Marathi); Koya, Tentuli (Oriya); Imli (Punjabi); Chinta (Telugu) (Mishra,1997).

2.6. Chemical constituents of seeds of T. indica

Phytochemical investigation carried out on T. indica revealed the presence of many active constituents, such as phenolic compounds, cardiac glycosides, (Rasu et al., 1989) (-) mallic acid, (Kobayashi et al, 1996) tartaric acid, the mucilage and pectin, arabinose, xylose, galactose, glucose, and uronic acid (Ibrahim and Abbas, 1995). The ethanolic extract of T. indica showed presence of fatty acids and various essential elements like arsenic, calcium, cadmium, copper, iron, sodium, manganese, magnesium, potassium, phosphorus, lead, and zinc (Samina et al., 2008). The pulp contains organic acids, such as tartaric acid, acetic acid, citric acid, formic acid, malic acid, and succinic acid; amino acids; invert sugar (25-30%); pectin; protein; fat; some pyrazines (trans-2-hexenal); and some thiazoles (2-ethylthiazole, 2-methylthiazole) as fragrant; and the seed polysaccharides are found with a main chain consisting of β-1,4-connected glucose molecules together with xylose (α-1, 6) and galactose; total protein; lipids with fatty oils; and some keto acids. The major fatty acids of seeds were palmitic acid, oleic acid, linoleic acid, and eicosanoic acid. The unsaponifiable matter from the seed oil of T. indica showed presence of β-amyrin, compesterol, β-sitosterol and seven hydrocarbons. T. indica seeds and pericarp contain phenolic antioxidants. The profile of polyphenols in Tamarind pericarp was dominated by proanthocyanidins in various forms, such as apigenin, catechin, procyanidin B2, epicatechin, procyanidin dimer, procyanidin trimer, along with taxifolin, eriodictyol, naringenin, of total phenols, respectively. The
content of Tamarind seeds comprised only procyanidins, represented mainly by oligomeric procyanidin tetramer, procyanidin hexamer, and procyanidin pentamer with lower amounts of procyanidin B$_2$ epicatechin (Sudjaroen et al, 2005).

**2.7. Medicinal and pharmacologic properties of *T. indica***

**2.7.1. Antidiabetic activity**

An aqueous extract of seeds had a potent antidiabetic activity in STZ induced diabetic male rats. The extract was given to mild diabetic and severe diabetic rats, and hyperglycemia was significantly reduced, measured by fasting blood glucose levels (Maiti et al., 2004). Similarly, hyperlipidemia was found to be reduced, measured by different contents of cholesterol. This rat model may shed some light on the basis of ancient herbal therapy in India (Maiti et al., 2005).

**2.7.2. Antiinflammatory and analgesic activity**

A bark is used in the treatment of pain traditionally, and to prove this scientifically, suitable animal screening models were used, such as hot plate test and acetic acid induced writhing test at the dose of 50 mg/kg, i.p. Petroleum ether extract showed significant increase in reaction time as compared with other extracts. Preliminary phytochemicals test showed presence of sterols and triterpenes in the extract; hence these compounds might be responsible for analgesic activity (Dighe et al, 2009). Leaf juice with ginger is used in the treatment of bronchitis and the bark dried and pounded and added to water for the treatment of eye inflammation (Irvine, 1961).

**2.7.3. Antimicrobial activity**

The methanolic leaf extract was assessed for antibacterial activity against *Burkholderia pseudomallei*, and its *in vitro* inhibitory potential suggests further animal studies to understand the role of *T. indica* in treating melioidosis (Muthu et al., 2005). The antimicrobial activity of the concentrated extracts (aqueous, ethanolic, acetone) was evaluated by determination of the diameter of zone of inhibition against both gram-negative and gram-positive bacteria and fungi using the paper disk diffusion method. These reported to possess potent antimicrobial activity against *Salmonella paratyphi*, *Bacillus subtilis*, *Salmonella typhi*, and *Staphylococcus aureus* (Doughari, 2006). Methanol and acetone extracts have shown significant antimicrobial activity against *Klebsiella pneumonia* by agar disk diffusion method (Vaghasiya et al., 2009).
2.7.4. Antioxidant properties

The seed and pericarp contain phenolic antioxidant compound (Sudjaroen et al., 2005). All the extracts exhibited good antioxidant activity (64.5-71.7%) against the linoleic acid emulsion system compared to synthetic antioxidants, butylated hydroxyl anisole and ascorbic acid (Siddharaju, 2007). Thai Tamarind seed coat using solvent extraction with ethanol was found to be the most active in terms of peroxide value (Luengthanaphol et al., 2004). Ethanolic extract of fruit pulp showed significant antioxidant and hypolipidemic activity in hypercholesterolemic hamsters (Martinello, 2006). Antioxidant activity of ethanolic extract of seed coat were assessed by DPPH (2,2-diphenyl-1-picrylhydrazyl) free radical scavenging method using ascorbic acid as a standard. This activity of extract may be attributed to its free radical-scavenging ability (Vyas et al., 2009).

2.7.5. Antivenom activities

In the Indian traditional medicine, various plants have been used widely as a remedy against snake bite. In a study, the effect of *T. indica* seed extract was investigated for its pharmacologic and enzymatic activity, where, it inhibited phospholipase A, protease, hyaluronidase, L-amino acid oxidase, and 5'-nucleotidase enzyme activities of venom in a dose dependent manner (Al-Fatimi et al., 2007). The extract neutralized the degradation of β-chain of the human fibrinogen and the indirect hemolysis caused by the venom. The extract prolonged the clotting time moderately, and myotoxic effects, such as edema and hemorrhage, induced by the venom at different doses; hence *T. indica* extract is an alternative for the serum therapy (Ushanandini et al., 2006).

2.7.6. Effect on cardiovascular system and blood

In Bangladesh, fruits were evaluated for their effects on the lipid profile, systolic and diastolic blood pressure, and the body weight of humans (Iftekhar et al., 2006). In hypercholesterolemic hamsters, the effect of the crude extract from the pulp was investigated on lipid serum levels and atherosclerotic lesions. Tamarind extract has a high potential in diminishing the risk of atherosclerosis in humans (Martinello et al., 2006). Another experimental study on hamsters has shown that the hydroalcoholic extract of Tamarind pulp influenced the mediator system of inflammation (Librandi et al., 2007).

2.7.7. Effect on cellular system

The L-(-)-Di-n-butyl maleate was isolated from methonolic extract of fruit and it exhibited a pronounced cytotoxicity against sea urchin embryo cells. In comparing structure-activity
experiments, this toxicity is connected with the special structure of the chemical. Only L(-)-Di-n-pentyl maleate was a stronger inhibitor (Kobayashi et al., 1996). In the descending colon of Swiss albino mice, the fruit pulp caused a greater rate of cell proliferations than in the ascending part, when they were fed a diet of the pulp, compared with the negative controls (Shivshankar et al., 2004). A polysaccharide isolated and purified from T. indica showed immunomodulatory properties like phagocytic enhancement and inhibition of leukocyte migration during cell proliferation (Sreelekha et al., 1993). Phenolic flavonoids from the seed coat extract showed inhibitory effect on nitric oxide production. In a murine macrophage-like cell line RAW 264.7 and in mouse peritoneal macrophages the extract significantly attenuated the nitric oxide production, in a concentration dependent manner (Kumutarin et al., 2004).

2.7.8. Effect on enzyme

Proteinase inhibitors with high inhibitory activity against human neutrophil elastase were found in seeds. A serine proteinase inhibitor denoted PG50 was purified using ammonium sulfate and acetone precipitation activity, showed that PG50 preferentially affected elastase release by platelet activating factor stimuli and this may indicate selective inhibition on platelet activating factor (PAF) receptors (Fook et al., 2005). Other bioinsecticidal studies included both in vivo and in vitro studies. In an in vitro investigation about insect digestive enzymes from different orders of Coleoptera and Diptera, a proteinaceous inhibitor from seeds showed remarkable activity. In an in vivo bioinsecticidal assay, larvae were fed seed-incorporated artificial diets. The concentration of Tamarind seed added to cause 50% mortality (LD$_{50}$) was 3.2%. The addition of 4% seed caused a mortality of approximately 34% (Araujo et al., 2005). Neuraminidase from Clostridium chauvoei (jakari strain) was reduced in its activity in a dose dependent manner by a partially purified methanolic extract (Useh et al., 2004).

2.7.9. Helminthes infections (parasitic worms)

The leaves are used in the extraction of Guinea worms, and afterward in the treatment of wounds, left by the parasite (Keita et al., 1993). Macerate of the seeds is used as vermifuge (Floch et al., 1985), and also the fruits are used for this purpose. An extract of the leaves and the root is used to treat ankylostomiasis (hookworm) in some parts of Tanzania (Haerdi et al., 1964). The Tamarind pulp with lemon is used to treat diarrhoea, and the root is used to treat dysentery (Chhabra et al., 1987).
2.7.10. Hepatoprotective and antiasthmatic activity

Some experimental studies have predicted the antiasthmatic and hepatoprotective effect. The methanolic extract of leaves, exhibited significant antihistaminic, adaptogenic, and mast cell stabilizing activity in laboratory animals (Tayade et al., 2009). The aqueous extracts of different parts, such as fruits, leaves (350 mg/kg p.o.), and unroasted seeds (700 mg/kg p.o.) were administered and a significant hepatoregenerative effect was observed in animal model of hepatotoxicity (Pimple et al., 2007).

2.7.11. Laxative properties

The fruit is used traditionally as a laxative, due to the presence of high amounts of malic and tartaric acids and potassium acid (Irvine, 1961). Children in Madagascar are given whole Tamarind fruits for breakfast to overcome constipation. The laxative can be taken in the form of a sweetmeat, called Bengal by the Wolof people of Senegal, prepared from the unripe fruit of Tamarind and sometimes mixed with lime juice or honey (Dalziel, 1937). In Bamako, Mali, drinks are prepared from the pulp (Diarra, 1977) and in Burkina Faso, the fruits are crushed and soaked for half a day in water with a little salt before consumption (Kerharo et al., 1950). Abdominal pain is not a specific disorder but a complaint, which refers to a painful abdomen and which may have a wide variety of causes, including constipation or diarrhoea. Soaked fruits are also eaten by rural Fulani in Nigeria, to relieve constipation (Lockett et al., 2005). Roots, prepared as an extract, are used in the treatment of stomach ache or painful abdomen, mainly in East Africa (Chhabra et al., 1987), and also in Burkina Faso it is used in abdominal pain and related complaints (Kristensen et al., 2003). In Benin, the fresh bark of young stems is macerated for 24 h and taken orally as a purgative or for abdominal pain (Fandohan, 2007).

2.7.12. Malaria and fever

Fruits are known as a febrifuge in Madagascar (Norscia et al., 2006) whereas; in Ghana Tamarind leaves are used for the treatment of malaria (Asase et al., 2005).

2.7.13. Wound healing

It is often cited in the literature pertaining to the treatment of cuts, wounds, and abscesses. The bark or leaves are most commonly used and applied externally on the spot, either as a decoction or as a powder or poultice, alone or in combination with other species. In the medicinal plant market in Dakar, Tamarind bark is mostly sold for wound healing purpose, (Tignokpa et al., 1986) occasionally other plant parts are found in wound
healing medicine, such as the fruit (Tapsoba et al, 2006), the pod husks, (Kheraro et al., 1974) or the gum (Inngjerdingen et al., 2004). A decoction of leaves is one of the most important agents to clean wounds caused by Guinea worm infections (Fabiyi et al., 1993).