CHAPTER – II

REVIEW OF LITERATURE

The knowledge of herbals has accumulated over thousands of years so that we possess many effective means of ensuring health care. Numerous phytoconstituents are present in medicinal herbs as key components. Traditionally plants are the main sources of drugs.

Diabetes mellitus is a heterogenous metabolic disorder characterised by altered carbohydrate, lipid and protein metabolism (Das et al 1996). The management of diabetes is considered a global problem and successful treatment is yet to be discovered. The modern drugs, including insulin and oral hypoglycaemic agents, control the blood sugar level as longer they are regularly administered and they also produce a number of undesirable effects (Upadhayan et al 1996, Reynolds J.E. 1997). Treatment of diabetes has been attempted with different indigenous plants and polyherbal formulations (Joy KL and Kultan R, 1998). Interest in this area has lead to the study of medicinal plants to discover new drugs in the treatment of diabetes.

PATHOGENESIS OF THE TYPE II DIABETES

Type 2 diabetes is characterized by (i) defects in insulin secretion; (ii) insulin resistance involving muscle, liver and the adipocyte and (iii) abnormalities in splanchnic glucose uptake. Impaired insulin secretion is a
uniform finding in type 2 diabetes and evolution of beta cell dysfunction has been well characterized in diverse ethnic population (Defronzo RA, 1997) and role of insulin resistance is well established (Defronzo et al, 1988). This imbalance result in elevated fasting and post prandial glucose levels. If this imbalanced homeostasis does not return to normalcy and continues for a protracted period of time, it leads to hyperglycemia that in due course turns into a syndrome called diabetes mellitus. There are two main categories of this disease-type I diabetes mellitus also called IDDM (Insulin dependent diabetes mellitus) and it is a heterogenous and polygenic disorder, with a number of non-HLA foci (about 20) contributing to the disease susceptibility (Defronzo RA, 1997).

The type 2 diabetes is complicated into several factors inherent to disease process such as insulin resistance, hyperinsulinemia, impaired insulin secretion, reduced insulin mediated glucose uptake and utilization (Baron et al 1987; Polonsky et al, 1996; Bonner and Weir 2001, Wangot et al, 1982).

The progression from normal to Impaired glucose tolerance (IGT) to type 2 diabetes with mild fasting hyperglycemia (>120-140 mg/dL, 6.7-7.8 mmol/l) is characterized by hyperinsulinemia which is the starting point of this disorder. When the fasting glucose exceeds 120 mg/dL there is a progressive decline in fasting and glucose stimulated insulin levels, which is supported by decline in ß-cell function (Polonsky et al, 1994).

Studies employing the euglycemic insulin clamp, animal models and insulin suppression techniques have provided direct quantitative evidence that the progression from normal to impaired glucose tolerance is associated with
the development of severe insulin resistance (Berrish et al, 1995).

Englycemic insulin clamp technique was used to find the effect of insulin resistance on type II diabetes (Defronzo et al, 1979). The ability of glucose to stimulate its own uptake was also impaired in type 2 diabetes (Nelsen et al, 1998).

PHARMACOTHERAPY OF AGENTS USED IN DIABETES

Until 1995, insulin and sulfonyl ureas were the only classes of drugs available for the treatment of diabetes. Since then, insulin analogues a new sulfonylurea and four new classes of antidiabetic agents have been approved for use. Glycemic targets, life style intervention and available classes of antidiabetic agents are applied in the progressive management of diabetes, though these agents produced several adverse effects.

Insulin has been widely used since 1920’s. Subcutaneous insulin injection in type 2 diabetes supplement the body's natural production of insulin, both in the basal state and post prandially (Richard et al, 1993). Most insulin used now-a-days is of recombinant human origin (Strattom et al, 2000). Adverse events associated with insulin include weight gain, hypoglycemia and rare allergies or irritation at the site of injection (Bloomgarden ZT, 1999).

The sulfonylureas available since 1940's are one of the two classes of insulin secretagogues. These agents bind to the sulfonylurea receptor on pancreas cells, leading to changes in membrane electrophysiology. The first
generation sulfonylureas (Marks et al, 2000) are not frequently prescribed because of their lower potency and the resulting higher risk of adverse effects and drug interaction. The sulfonylureas may also increase the cardiovascular risk, in patients with diabetes as a result of their activity on vascular and cardiac sulfonylurea receptors.

The meglitinides are agents which also bind with sulfonylurea receptors, but they have better binding characteristics, produce faster and brief stimulus to insulin secretion. They produce less hypoglycemia and weight gain than sulfonylureas (Burge and Schede, 1997). The Biguanides available for therapy are metformin, phenoformin and fenoformin. Fenoformin was removed because of the adverse effects produced (Bell and Hadden, 1997). Its major activity is to reduce hepatic insulin resistance and increase glucose production, but precise mechanism is not known. The most common adverse effects of biguanides are gastrointestinal disturbances, altered taste and rarely lactic acidosis (Chan et al, 1999).

Thiazolidinediones or glitizones approved for therapy are pioglitazone, rosiglitazone and troglitazone. There agents are believed to work through binding and modulation of the activity of a family of nuclear transcription factors termed PPARs (Hashimoto and Fujiwara, 2000). They help in glycemic control over weeks to months in parallel with an improvement in insulin sensitivity and reduction of free fatty acid levels. The adverse effects of glitazones were weight gain and fluid retention. Troglitazone has been withdrawn from use since it has produced rare fatal
hepatotoxicity.

The alpha-glucosidase inhibitors are agents which work to inhibit the terminal step of carbohydrate digestion at the brush border of the intestinal epithelium, which allows the sluggish insulin secretion dynamics of type 2 diabetes to catch up with carbohydrate absorption (Lebovitz HE, 1997). The two available agents are acarbose and miglitol. Their use has been limited by a number of factors, including the need for dosing at beginning of each meal, flatulence and modest glucose-lowering efficacy.

PLANTS AND MINERALS IN THE THERAPY OF TYPE 2 DIABETES

Botanicals and minerals are an important source of new therapies for type 2 diabetes and insulin resistance. To date a number of medicinal plants are reported to have antidiabetic activity, but only a scant few have been subjected to rigorous scientific evaluation for safety and efficacy in humans (Oubre AY et al, 1997). The popular among them are tabulated in Table – 1. Many nutraceuticals and metal ions are used in the management of diabetes mellitus. The prominent among them are tabulated in Table – 2.
SELECTION OF DRUGS FOR THE PRESENT STUDY

A preliminary ethno-medical survey was conducted in and around Pondicherry on the use of traditional herbal formulations used in the treatment of diabetes mellitus. Patients, physicians of the Indian system of medicine and the general public were interviewed. During the survey it was observed that a number of siddha formulation are used in the management of diabetes mellitus.

These formulations which were used in current practice and the formulation which were official were assessed through a thorough literature review. Literature survey revealed that a number of siddha antidiabetic formulation which were popular were hither to scientifically unexplored. Hence it was thought worth to select such formulations for a detailed scientific study. The literature review lead to the selection of two reputed siddha formulations, which are described in recognized siddha text and were traditionally used in the treatment of diabetes mellitus.

The selected formulation belong to the class of agamarundhu (internal medicine) viz Bhasmas or parpams and Uchidums. The uchidum formulation (FS002) and parpam formulation (NP003) were herbal and herbo-mineral in nature respectively.

The raw materials of the uchidum (FS002) formulations are (Anuboga Vaidya Navanetham, Onpatham Patham)

- Bark of *Ficus racemosa Linn* (Family - *Moraceae*)
- Sesame cake (Mare of sesame seeds - *Sesamum indicum* Family – *Pedaliaceae*).
The parpam formulation (NP003) contains the following ingredients (Siddha formulary, 1993).

i. Purified zinc

ii. Leaf juice of *Eclipta alba* (Family - *Compositae*)

iii. Pulp of aloe leaf-*Aloe vera* (Family - *Liliaceae*)

**REVIEW OF INGREDIENTS OF THE FORMULATIONS**

*Ficus racemosa Linn.* (Family - *Moraceae*)

**Introduction**

Synonym: *Ficus glomerata* Roxb.

English names: Cluster fig, Country fig, Gular fig.

Vernacular names: Hindi - Gulav, Umar; Kannada - Atti; Malayalam - Atti, Athimaram; Tamil - Atti, Aththi; Telugu - Bodda, Paidi, Udumbaramu.

**Traditional use**

**Part of the plant : ethnic claim**

(i) *Root-extract:* in diabetes, dysentery

(ii) *Latex:* on boils, on adenitis, muscular pain, pimps, scabies, piles and pulmonary diseases

(iii) *Fruit:* in pulmonary diseases

(iv) *Bark-juice:* on boils, in adenitis axillaris, epidydimitis, hydrocele,
orchitis;

(v) *Juice of pith*: in menorrhagia, spermatorrhoea;

(vi) *Leaves*: in small pox;

(vii) *Leaf gall (decoction)*: for washing septic wounds;

(viii) *Bark and Fruit* (together): in urinary complaints;

(ix) *Fruit*: in diabetes and carminative

*RIGVEDA*: cures piles, internal wounds, removes impurities from blood, worms from alimentary canal; *YAJURVEDA*: bark kills worms; *ATHARVAVEDA*: useful in skin diseases, including leprosy, sinus, oedema, impurities of blood and in piles; *MADANADINIGHANTU*: useful in antifertility, pimples and wounds; *BHAVAPRAKASHA*: useful in treatment of pimples and wounds; *DANVANTARINIGHANTU*: removes worms, cures thrombophlebitis, syncope, burning sensation and unusual thirst; *KAIYADEVANIGHANTU*: astringent, sweet and heavy, cures pimples and wounds, diseases caused by deranged phlegm and deranged bile; fruits are tasteful, invigorating, astringent, cooling, cardiac tonic, useful in urinary diseases, bile disorders, menstrual disorders.

*AYURVEDA*: *Latex*: external application useful in cuts, insect bites, boils, bruises, swellings, while internal application is beneficial in haemoptysis, bleeding piles and menstrual problems.

*SIDDHA*: (i) *Bark*: used to prepare the drug *atti pattai*, (ii) *Latex*: for *atti pal*, and (Hi) *Leaf*: an ingredient of *atti ilai*. 
**Modern use**: Stem-bark (50% EtOH extract): anti-inflammatory, anti protozoal, hypoglycaemic; *Leaf-powder*: useful in bilious affections; *Leaf-gall*: beneficial in small pox.

**Phenology**: *Flowering*: Spring; *Fruiting*: Rainy season.

**Distribution**: Throughout India; Pakistan, Bangladesh, Sri Lanka.

**Ecology and cultivation**: Tropical plant; grows on the banks of streams, sides of ravines, on rocky slopes, up to 1500 m; wild (Fig.1.1).

**Morphology of Ficus racemosa**

Tree 12-20m; dark brown, branchlets white-pilose leaves alternate, ob lanceolate, 9-20 x 3-6 cm, sub coviaceous, lateral nerves 8-10 pairs, somewhat flattened and prominent on both sides, intercoastals obscure, blade glaucous above, glaucous below, base rounded to acute, margin entire, apex acute, petiole not articulate, glandular at the basal nerve-axils, 3-5 cm; stipules lanceolate, 1-1.5 cm long figs, monoecious, cauliflovons, (sub globose, 1.5-2.5 cm across, white-pilose; fig wall thick, soft, ripening purplish red; peduncle upto 7mm; basal bracts ovate-triangular upto 2mm, obtuse, persistent, orifice subumonete or slightly sunken, closed by 5-6 bracts; internal bristles, perianth shortly cupular; tepals 3-5; ovate-lanceolate, 1.5mm, sacrious, lacerate, acute, ostiolar, pedicel upto 3 mm.

Stamens 2, exserted; filaments 1mm, connate below anthus oblong,
parallel 0.8mm ovary versile or shortly stalked browish, 1.5 mm style upto 3 mm. Gall flower similar, long stalked; style short achenes lenticular (Fig.1.2).
Biological activities and compounds reported from *Ficus racemosa* Linn

Siddiqui et al (1996) studied the ethnomedical uses of plants and reported that the latex of *Ficus racemosa* bark could be used for treatment of inflammation and reddening of eyes.

Aktar M.S. (1992) studied some indigenous medicinal plants traditionally used as antidiabetic drugs and reported that the dried fruits of *Ficus racemosa* was effective against diabetes and significantly produced hypoglycemic activity in alloxan induced diabetes.

Kar et al (1999) reported that the calcined root of *Ficus racemosa* and its ethanolic extract produced significant antihyperglycemic activity on streptozotocin induced diabetes at doses of 90 mg/kg and 250 mg/kg.

Pereira et al (1984) screened for biological activity of different plant parts and they studied the effect of bark of *Mangifera Indica* and *Ficus racemosa* boiled in coconut oil on skin ulcers and fistula.

Ojha et al (1983) reported that the dried bark powder of *Ficus racemosa* exhibited anti hyperglycemic activity in human volunteers.

Srivastava et al (1962) reported that the bark and latex exhibited significant antifibrinolytic activity and anticoagulant activity.

Mokkhasmit et al (1971) studied the roots of *Ficus racemosa* and reported that it exhibited significant antihistaminic, antipyretic and antispasmodic activity.

Jain and Tarafder (1970) compiled ethnomedical data of medicinal plants used by santals and in that reported that the bark of *Ficus racemosa* were used for the treatment of spermatorrhoea, menorrhagia and lactation failure.

Mukherjee et al (1996) prepared a herbal uterine tonic with the bark of *Ficus racemosa* and showed that it could be used for the treatment of menorrhagia.

Forestieri et al (1996) reported that the leaf extract of *Ficus racemosa* exhibited significant analgesic; antiinflammatory and antipyretic activity in
rodents in the dose of 0.5 g/kg body weight.

Merchant et al (1979) conducted chemical investigation of the fruits of *Ficus glomerata* (*Ficus racemosa*) and reported the presence of the phytococonstituents such as Lanosta-8-22-Dien-3-Beta-one, Lupeol acetate, and β-sitosterol.

Singhal and Saharia, (1980) has studied the phytococonstituents of *Ficus glomerata roxb* and reported the presence of lupeol, lupeol acetate, β-sitosterol and stigmasterol in the trunk bark.

Dey (1998) has given a brief account of *Ficus racemosa Linn* and mentioned about the Ayurvedic preparation, Udum barasar. This preparation is analgesic, astringent, carminative, diuretic, stimulant, supportive and tonic. The bark is also useful in bilious affections, diabetes, dropsy, dysentery, diarrhoea, menorrhagia, haemoptysis, seminile decay and small pox. The root is given to the cattle for rinder pest.

Narayana Aiyar et al (1957) have studied the barks of *Ficus religosa*, *Ficus bengalensis*, *Ficus glomerata* *Ficus retusa* and *Ficus tsiela*. They also compared the barks of all these species and brought out the differences among them.

Druley (1973) in his useful plants of India has given a wealth of information on the description, medical uses and economic uses of eight species of *Ficus*, namely, *Ficus racemosa*, *Ficus banghalensis*, *Ficus carcia*, *Ficus elastica*, *Ficus excelsa*, *Ficus angusitifolia*, *Ficus religiosa* and *Ficus*
Druley attributes the bark of the trunk as antidiabetic.


Mitra and Mehrotra (1982) made comparative pharmacognostic study on the leaf and bark of *Ficus amplissima*.

Saeed and Khan (1996) made comparative cytomorphological and irritation studies of some Ficus species (*Ficus benghalensis, Ficus infectoria, Ficus hispida* and *Ficus religiosa*).

Mandal et al (2001) made pharmacognostic studies on *Ficus hispida*. Mitra and Kapoor (1974) studied the pharmacognosy of *Ficus tsiela*, they also studied the pharmacognosy of *Ficus tsiela*, they also studied *Ficus lacor* (Mitra & Kapoor, 1974), Pharmacognosy of *Ficus virens* was studied by Mitra and Mehrotra (1980).

The literature survey reveals that the previous pharmacognostic studies on *Ficus racemosa* was not complete and was not carried out in a scientific systematic manner. So from an industrial view point, to establish quality control parameter for the raw materials, the present investigation was carried out. The present investigation provides detailed information on the anatomy of the bark of *Ficus racemosa* (*Ficus glomerata*) and adds further to the knowledge of the bark of the important tree, which is valued both economically for its edible fruit and timber and for medicinal purposes.
Biological activities of related Ficus species

*Ficus benghalensis*

Angusti et al (1994) studied the hypoglycemic effects of *Ficus benghalensis* Linn (Indian banyan tree). Leucodelphindin and Leucopelargonin derivatives isolated from the bark produced hypoglycemic action, and reduced lipid levels in normal and alloxan diabetic rats and dogs.

Bark showed hypoglycemic activity in both normal and alloxan diabetic rats (Pandey et al., 1960). LD$_{50}$ of the plant extracts in mice was 9.47 g/kg by I.P. route. Two compounds Friedalin and β-sitosterol were isolated from leaves (Singh et al, 1968).

Sheeja Cherian et al (1992) showed that oral administration of dimethyl ether of Lencocyanidin-3-O-β D-galatosyl cellubioside isolated from the bark decreased blood and urine sugar, certain lipid components in serum and tissues and glucose-6-phosphate activity in liver and hypoglycemic responses were enhanced when it was given with low dose of insulin.

Shukla et al (1994) studied the hypoglycemic effects of aqueous extract of *Ficus bengalensis* in alloxan recovered, mildly diabetic and severely diabetic rats and the extract showed significant biological activity.

Shukla et al (1995) studied the aqueous extract of the bark of *Ficus benghalensis* which lowered total cholesterol, LDL-cholesterol and triacyl glycerol on one hand and increased HDL cholesterol on the other hand in serum of rabbits fed with cholesterol for more than a month.
**Ficus carica**

Four compounds such as taraxasterol, β-sitosterol, lupeol, β-amyrin along with bergapten were isolated from leaves (Singh et al., 1962). The bark of extract have varying degree of relaxant and spasmolytic effects on various smooth muscles.

**Ficus religiosa**

β-sitosterol-D-glucoside isolated from *Ficus religiosa* bark injected I.V in rabbits at 50 mg/kg and 75 mg/kg body weight doses decreased blood sugar by 23.2 and 33.8% respectively (Chopra et al., 1967).
**Introduction to *Sesamum indicum***

*Sesamum indicum L.* (Family: Pedaliaceae)

*Sesamum indicum* L. is an annual herb native to the tropics and the plant grows erect and reaches a height of 1 to 2 m, with fine pubescent leaves, pale rose or white flowers and a capsule type fruit (Fig.1.3).

**Synonym**: *Sesamum orientale* L., Gingilly, till.

**Vernacular names**: English – Sesame, Tamil – Ellu, Telugu – Noogulu

**Habitat**: Cultivated beds

**Constituents**: Oil contains sesamin, sesamolin, olein, stearin, palmitin, myristin and linolein. Alanine, arginine, phenylalanine, vitamin B1 and vitamin E were also present.

**Medicinal uses**

- **Leaves**: Astringent, demulcent and emollient
- **Seed**: Diuretic, emollient, galectogogue, tonic, chronic dry constipation, dental caries, treatment of haemorrhoids and ulcers.
- **Seed oil**: Laxative, tonic and pharmaceutical solvent.

**Biological activity of *Sesamum indicum***

Dhar et al (1968) studied the cytotoxic activity of ethanolic extract of sesame seeds in CA-9KB cells and reported that the extract has significant cytotoxic and antibacterial activity and the ED$_{50}$ was found to be 20 mcg/ml.
Saha et al (1961) studied the ecobolic and abortificient properties of *Sesamum indicum* seeds. Reddy et al (1989) reported that leaves of *Sesamum indicum* ground with jaggery is used ethanomedically in the treatment of diabetes in Ananthapuram district of Andhra Pradesh, India.

Singh and Ali (1989) studied the folk medicines of Aligarh district of Uttar Pradesh, India and reported that leaves of *Sesamum indicum* were used to control diabetes.

Singh and Joshi (1983) studied the antihyperglycemic and hypocholestremic properties of ginger and sesame seeds and reported that ethanolic extracts, produced significant anti-hyperglycemic and hypocholestremic activity.

Fukuda et al (1985) reported that the acetone extract of sesame seeds showed significant antioxidant activity at the concentration of 0.2% in linoleic acid substrate system.

Feinstein and Ringel (1951) isolated sesamin from sesame oil and patented the procedure. Lignan compound and their manufacture from sesame seeds were demonstrated by Mimura et al, 1997 and they isolated lignan such as sesamin and sesamolinol.

Kawagishi et al (1994) studied the antioxidant effect of pinoresinol glycoside isolated from sesame seed extract and the activity was patented.

Anila and Vijayalakshmi (2000) studied the beneficial effects of flavonoid fraction from *Sesamum indicum* seeds and reported that the fraction showed significant hypocholestremic activity, when administered orally to
albino rats at the dose of 10 mg/kg body weight.

Pedalin, a flavonoid (Jain SC, 1981) was isolated from *Sesamum indicum* seeds and the concentration of pedalin was found to be 0.5%. Lignans like sesamin 0.0016% (Fukuda et al., 1985), sesaminol (Katzuzaki et al, 1994) and sesamolinol (Osawa et al., 1985) were also isolated from sesame seeds. 3.9% of arginine was found in sesame cake (Ramachandra BV, 1957). The sesame seeds also showed the presence of α-tocopherol (Mannan and Ahmad, 1966) and β-sitosterol in appreciable quantities.

The sesame seeds also exhibit emmenagogue (Saha et al., 1961), galactogogue (Singh and Ali, 1989) antiulcer (Singh et al., 1980) and cytotoxic properties (Vlietinck et al., 1995).

The hot aqueous extract of seeds were used ethano-medically for the treatment of piles and the seeds also have antiviral properties (Singh et al, 1980 and Vlietinck et al., 1995).

*Aloe vera*

**Introduction to Aloe vera**


Family : *Liliaceae*

English names : Barbados aloe, Curacas aloe, Indian aloe, Jafarabad aloe.

Vernacular names : **Hindi** - Ghee kunvar; **Kannada** - Lolesara;
Malayalam - Kattarvazha kumari; Tamil - Alagai, Katralai, Chirukuttali, Kuttilai; Telugu - Chinnakata banda, Kala banda, Kittanara.

**Traditional use**

**Part of the plant/Ethnic claim**

*Leaf-pulp*: In liver troubles, jaundice, fever, gonorrhoea, spleen disorder, rheumatism, piles, dysmenorrhoea, sterility in women;

*Leaf-mucilage*: Mild laxative, to cure hardening of breast tissues, in insect stings.

*AYURVEDA*: alternative, bitter, cooling, purgative, sweet, tonic, anthelmintic, useful in eye diseases, tumours, enlargement of spleen, liver troubles, vomiting, skin diseases, biliousness, asthma, leprosy, jaundice, strangury, ulcer; *Flowers*: anthelmintic.

*UNANI*: Gheekawar is useful in inflammation of spleen, lumbago, muscular pain, ophthalmia, digestive, purgative; *Leaves* good for piles and biliousness.

Modern use: *Aloe*: in menstrual diseases, stomach pain, tonic after pregnancy, uterine disorders, high fever; *Pulp*: menstrual suppressions, nervous imbalance; *Aloe compound*: in treatment of women sterility; *Mucilage*: painful inflammation; *Root*: colic pain; *Aloe mixture with other plant extracts*: for treating obstruction of lymphatic system.
**Phytography**: A coarse-looking plant with a short (30-60 cm high) stem; leaves succulent, green, large (37 cm long, 10 cm broad, 2 cm thick), densely crowded; flowers in racemes, bright yellow, tubular, stamens frequently projected beyond the perianth tube (Fig.1.4).

**Phenology**: *Flowering*: September-December; *Fruiting*: scarce.

**Distribution**: A native of North Africa, Canary Islands and Spain; naturalised in India; many varieties are found in a semi-wild state in all parts of India; also cultivated in pots and gardens.

**Ecology and cultivation**: Xerophyte; propagated by suckers.

**Chemical contents**: Aloin, aloe-emodin and resins.

**Adulterant**: *Aloe candelabrum* Berger is used as substitute for *Aloe barbadensis* Miller.

**Biological activity of Aloe vera**

The dried sap of the aloe plant (aloes) is a traditional herbal remedy frequently used to treat dermatitis, burns and to enhance wound healing (Vogler and Ernst, 1999), and one variety of this plant is used for diabetes in India (Grover et al, 2002) and the Arabian peninsula (Al Rowais, NA, 2002). Its ability to lower the blood glucose was studied in 5 patients with type 2 diabetes (Ghannam et al, 1986). Following the ingestion of aloe (one-half a teaspoonful daily for 4-14 weeks), fasting serum glucose level decreased in every patient from a mean of 273 ± 25 (SE) to 151 ± 23 mg/dL (P < 0.05) with
no change in body weight. This glucose-lowering activity has been confirmed in two other studies which reported that oral administration of the aloes juice (1 tablespoon twice daily) reduced fasting glucose and triglycerides in subjects with type 2 diabetes both in the absence and presence of concomitant sulfonylurea therapy (Yongchaiyudha et al, 1996; Bunyapraphatsara et al, 1996). No adverse effects were reported in these studies. Aloe gel also holds the potential for glucose-lowering activity, as it contains glucomannan, a water soluble fiber that reportedly has glucose-lowering and insulin sensitizing activities (Vuksan et al, 1999). The potential clinical efficacy of this plant warrants further study.

**Zinc**

Zinc is another essential mineral in human nutrition with a wide range of biological functions. Zinc fulfills catalytic, structural, or regulatory roles in more than 200 zinc-requiring metalloenzymes (Anonymous, 2001). The interaction of zinc with insulin induces conformational changes and enhances binding to the insulin receptor (Faure et al, 1992; Arquilla et al, 1978). With regard to glucose metabolism, zinc is a co-factor of several key enzymes. Zinc is an activator of fructose-1-6-bisphosphate aldolase, and an inhibitor of fructose-1-6-biphosphatase (Salguerio et al, 2001). Zinc can also exert antioxidant activity (Disilvestero RA, 2000), and is a cofactor in copper/zinc superoxide dismutase, a major antioxidant enzyme (Zelko et al, 2002). Some studies have reported zinc deficiency along with alterations in zinc metabolism in patients with diabetes (Salguerio et al., 2002; Disilvestero RA, 2000).
**Eclipta Alba**

**Introduction**

Synonym :  *Eclipta prostrata* (L.) Hassk.

Family :  *Compositae*
English name : Trailing eclipta.

Vernacular names :
- **Hindi** - Babri, Bhangra, **Kannada** - Garga;
- **Malayalam** - Kannunni, Kaiyanni, Kayyonni;
- **Tamil** - Garuga, Kaikesi, Karipan, Kayyantakara;
- **Telugu** - Galagara, Guntagalyeru.

**Traditional use**

**Part of the plant : Ethnic claim of the different parts of the plant**

*Leaf*: in gastric troubles, hepatic disorders

(i) *Stem-decoction*: in liver enlargement;

(ii) *Leaf-extract*: in fever and cough;

(iii) *Whole plant*: in hepatic problems, spleen troubles, antidote in scorpion sting. Whole plant in jaundice;

(iv) *Root*: in ulcers and wounds;

(v) *Leaf*: in sores, ulcers, wounds, spleen disorders;

(vi) *Whole plant*: in jaundice, spleen disorders;

(vii) *Leaf*: in leucoderma, skin diseases;

(viii) *Leaf*: in malaria;

(ix) *Whole plant*: in liver complaints;

(x) *Leaf*: for promoting hair growth.
**BHAVAPRAKASHA**: cures problems caused by phlegm and wind, beneficial for hair, skin, teeth and eyes, removes worms, and also effective in jaundice and oedema; **RAJANIGHANTU**: beneficial for hairs, eyes, oedema and phlegm; **KAIYADEVANIGHANTU**: it removes the problems caused by phlegm and wind and worms, beneficial for hair, teeth, skin, cures cough, jaundice and oedema; **NIGHANTURATNAKARAM**: in addition to the above qualities, this plant invigorates sex; **VAIDYAMANORAMA**: drinking juice of the plant strengthens the body and secures the foetus in womb.

**AYURVEDA**: cures headache, migraine; leaves are beneficial for hairs, they remove lice, blacken skin, cure pyorrhoea, chronic dysentery, oedema, nervous weakness, jaundice, anorexia, gum troubles and remove intestinal worms.

Modern use: *Herb*: in skin diseases; *Gum resin* (from herb): anticancerous against *Ehrlich ascites carcinoma*; *Plant*(50% EtOH extract): antiviral, spasmogenic; *Plant*(aqueous extract): ovicidal against *Sitotroga cerealella* eggs, nematicidal, haemostatic, beneficial in body inflammation, protective against hepatotoxic action of carbontetrachloride in female guineapigs; *Plant* (powder): curative of infective hepatitis, jaundice and viral hepatitis; *Leaf*(aqueous extract): myocardial depressant, hypotensive; *Leaf-juice*: cures shoulder pain caused by heavy load.

**Phytography**: Erect or prostrate diffused annual herb with roots at each node; leaves opposite, sessile, oblong-lanceolate, 1.0 - 2.5 cm long, very variable in form and width; heads subglobose, ±1.25 cm broad; flowers white
and compressed (Fig.1.5).

**Phenology** : *Flowering* and *Fruiting*: throughout the year, peak period - August-February.

**Distribution** : Throughout India, ascending up to 2000 m; Bangladesh and Pakistan. Ecology and cultivation: Common on damp wastelands, low waterlogged areas, roadsides, grassy humid localities, prefers warm climate; wild.

**Chemical contents** : *Leaf*: stigmasterol, a-tetraethyl methyl wedelolactone, di-methyl-wedelolactone, small amount of 2-formyl-terthienyl.

**Adulterants** : In Sanskrit literature, three types of *Bhringaraja* have been mentioned - white-flowered (*E. alba*), yellow-flowered (*Wedelia calandulacea*) and blue-flowered (not yet identified).
Fig.1.3 : Sesamum indicum L. – habitat

Fig.1.4 : Aloe vera – habitat

Fig.1.5 : Eclipta alba – habitat
Pharmacological screening for Diabetes mellitus

Animal model of diabetes have been widely used in biomedical studies, because they offer promising insight of mimiking human diabetes. Models of experimental diabetes exhibit many features of clinical diabetes. Hyperglycemia is the common feature in experimental models of diabetes (Bailey, 1949; Bell and Hye, 1983; Boquist, 1989). Either hypoinsulinemia or hyperinsulinemia may be noticed in experimental models of diabetes and other characteristics of clinical diabetes such as polydipsia, polyur, polyphagia and lethargy may appear in some models of diabetes (Bell and Hye, 1983).

Experimental models of diabetes, have been used not only for understanding the etiology of diabetes mellitus, but also for the investigation of mechanism involved in diabetic complications (Tomilinson et al., 1992). The experimental models used for induction of diabetes in animals and screening for antidiabetic activity are


b. Chemical diabetes (Ingle, 1948; Rakieten et al, 1963)

c. Spontaneous diabetes - Genetically predisposed to diabetes using chinese hamster (Meier and Yerganian, 1959).

BB wistar rat (Nakhooda et al, 1977)

Genetic hybrid mouse OB/DB (Hummel et al., 1966)

Maeaca nigra non human primate model (Howard, 1978)

d. Viral diabetes (Barrett - Connor, 1985).
**Chemical diabetes**

Various drugs and chemicals, have been reported to cause an experimental situation somewhat similar to diabetes (Ingle, 1948; Bartoy, 1949; Lithel and Berne, 1991). Among these diabetogenic substances alloxan and streptozotocin are the most specific and convenient ones, whereas others exhibit only a weak and reversible diabetogenic activity and their effects are not specific to pancreatic β-cells (Lithel and Berne, 1991).

The unique capability of alloxan to selectively destroy the pancreatic β-cells was first described by Dunn et al (1943). It was suggested that the diabetogenic action of alloxan may be due to mitochondrial dysfunction in β-cell (Boquist, 1989). More recently, it has been demonstrated that the interaction of alloxan with deoxyribonucleic acid plays an important role in the β-cell damage (Sakurai and Ogiso, 1995). Following the injection of alloxan, animals exhibit a transitory hyperglycemia followed in a few hours by hypoglycemia. The tendency of hypoglycemia gives rise in 24-48 h and then final hyperglycemia or diabetic state occurs (Bailey, 1949).

**Streptozotocin induced diabetes**

Rakieten et al (1963) were the first to demonstrate that streptozotocin when given intravenously produced diabetes in rats and dogs. Injection of streptozotocin (STZ) produced β-cell membrane damage (Orci et al, 1976) and depletion of nicotinamide dinucleotide in pancreatic β-cells (Gunnasson et al., 1974). Recent studies have suggested that STZ acts through the formation of carbonium ions, which cause alkylation of DNA (Eizink and Sandler, 1989).
STZ is probably the most widely used agent producing IDDM and NIDDM in experimental animals. These animals may exhibit most of the diabetic complications i.e. myocardial (Abede and Macheod, 1991), cardiovascular (Ozulikay et al., 1994), gastrointestinal (Oztusk et al., 1992), tracheal (Ozansoy et al., 1993), Kidney (Reddi et al., 1991), urinary bladder (Jeremy et al., 1993) and connective tissue dysfunction (Cohen et al., 1991).

The injection of STZ into the peritoneal cavity of 2-day old rats results in a NIDDM - like hyperglycemia state (Borner-Weir et al., 1981). In this model, STZ injection produces transient hyperglycemia rapidly develops that lasts for 2-4 days, and then for 6 week the plasma glucose remains at near-normal levels until approximately 6 weeks of age, takes to develop stable chronic hyperglycemia with plasma glucose concentrations ranging from 200 to 350 mg/dL. STZ induced NIDDM in rats constitute an invaluable pharmacological tool for antidiabetic drugs, because most of the diabetic patients are noninsulin-dependent in nature.

ANTIOXIDANT ACTIVITY

Molecular oxygen is an essential component of all living organism, but the formation of various reactive intermediates of molecular oxygen metabolises the cells aerobically, thus eventually leading to a process termed as oxidation. All the aerobic species suffer from injury if exposed to concentration more than 21% of oxygen (Halliwel B., 1996). Oxygen via its transformation to reactive oxygen species (ROS) i.e. OH⁻, H₂O₂, O₂⁻, can provoke uncontrolled reaction. The formation of ROS is enhanced with an increase in oxygen tension. Free radicals attack on double bond and alter biomolecules such as DNA, leading to deformity and crosslinking (Tripathi, Y.B., 1998).
The human body although continuously produces free radicals, it possesses several defense system which are constituted of enzymes and radical scavengers. The second line defense systems are constituted of repair systems for biomolecules which are damaged by the attack of free radicals (Davies, 1991). Specific enzymes are known to have been involved in this context and several of them have been identified in prokaryotes and eukaryotes. The functions of these enzymes involved in repairing directly damaged biomolecules such as lipids, polysaccharides, proteins and nucleic acids are well documented (Sohel and Weindrick, 1996).

The probable involvement of free radical attacks in aging and in some important pathological and degenerative processes leading to an accelerated aging, down's syndrome, alzheimer's disease, atherosclerosis, parkinson's disease, hepatic damage, hypertension, diabetes suppressed immune function, and retinopathy were well documented (Romacke and Renard 1996; Delattre and Rousellot D 1992; Nohl et al, 1997).

Antioxidants are compounds which act as inhibitors of oxidative process. They are quite large in number and diverse in nature, which oppose the process of oxidation largely by neutralising free radicals. Antioxidants at relatively small concentration have the potential to inhibit oxidative chain reaction.

The enzymatically potential antioxidants are superoxide dismutase, glutathione peroxidase, catalase and peroxidases (Cademes 1989). The non-enzymatic category are vitamin C, Vitamin E, Vitamin A, β-carotenoids, uric acid, ubiquinone and synthetic compounds like melatonin, Dihydro

Some plant products or extracts viz. extracts of ginger, onion, turmeric, capsicum, black pepper, long pepper, amla and tea beverages have also been reported to have anti-oxidant activity of non-enzymatic category (Martinez G, 2000).

**CLINICAL EVALUATION OF THE FORMULATIONS**

A clinical trial is defined as a prospective study comparing the effect and value of intervention(s) against a control in human beings. A properly planned and executed clinical trial is a powerful experimental technique for assessing the effectiveness of an intervention. In 1977 the Food and Drug Administration (FDA) in the USA divided the trial program into four phases:

**Phase 1**: In phase I studies clinical trials are conducted in volunteers in order to establish a rough idea of the dose to be administered. One of the main goal is to detect potentially harmful adverse effects and to determine the doses at which they occur. Basically it involves safety studies and also includes metabolic and pharmacokinetic studies.

**Phase 2**: In this studies the drug's potential therapeutic usefulness is evaluated in rigorously conducted trials by administering it for limited periods to small numbers of patients (50-100 patients) that must be as homogeneous as possible.

**Phase 3**: In this phase administration of the drug is extended to a larger and more varied patient population (around 1000-2000 patients). Here,
attention is turned to the question of the representativeness of the patients treated. Also duration of administration is increased and may last upto 6 or even 12 months with drugs intended for chronic administration. Finally, comparisons are undertaken with standard proven treatment modalities.

**Phase 4**: It is done after the new drug has been made commercially available. It encompasses very large scale studies under usual conditions of use, studies intended to detect, elucidate and if possible prevent rare and serious adverse effects that may have gone unrecognized in the clinical trials performed previously. Finally, additional more specific studies may be undertaken to investigate or increase knowledge of some pharmacological effects.

The type of clinical trial to be conducted or the type of design to be used were tailored to the specific clinical situation, the number of patients available, the disease state studied and a number of other factors.

**Types of Trials (WHO guidelines 2002)**

**Prophylactic Trials**

These are concerned with comparing the efficacy of preventive treatments, or of prophylactic measures administrated according to a strict experimental design on persons who are apparently not sick. Such trials are usually performed on volunteers. A control group is always necessary, whether the controls receive a dummy treatment, placebo or treatment of recognised efficacy. The main disadvantage of these trials is the ethical issues involved in the administration of drugs or vaccines to persons who are apparently not sick.
Therapeutic Trials

In this type of trial comparable groups or experimental units are drawn up and different treatment allotted at random to these units. With such a design, it is possible to infer significant effect of the treatment from differences observed between units after treatment. Many of the commonly done clinical trials are therapeutic trials.

Study designs in clinical trials (WHO guidelines, 2000)

Clinical research aimed at evaluating traditional medicine should incorporate the conventional concepts of research design, such as randomized controlled trials or other types of clinical studies, such as observational studies. The USA Food and Drug Administration guidelines for foods and dietary supplements, which introduce several types of clinical studies was thoroughly studied. The Guidelines for Good Clinical Practice produced by the International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use, as well as official guidelines from other governmental agencies may also be a good reference source for clinical research design.

Conventional concepts of clinical research design may be difficult to apply when using clinical research to evaluate various systems and practices of traditional medicine, depending on the goal of the assessment. In such circumstances, the choice of study design should be discussed on a case-by-case basis with experimental medical practitioners. The study design may be chosen from a whole spectrum of clinical research designs which are suitable
for assessing traditional medicine.

**Single-case design**

Single-case designs have the advantages of being adaptable to the clinical needs of the patient and the therapeutic approach of the practitioner, but have limitations due to their lack of generalization to other patients. Such designs are appropriate for the development of research hypothesis, testing those hypothesis in daily clinical practice and refining clinical techniques. Single-case designs using a common protocol, if the protocol can be systematically followed, should be advocated for collaborative research among practitioners from different backgrounds. For example, single-case designs can evaluate the effectiveness of various specialized acupuncture methods in patients with a variety of individual differences. In a single-case design, the patient is his or her own control. Treatment can be randomized for a patient, rather than the patient being randomized for a treatment.

**Black-box design**

The study of traditional medicine can also be undertaken in a "black-box" manner. This mean that the treatment and all of its components are delivered as they would be in the usual clinical situation. In this type of study, no component of the treatment "Package" is isolated and studied independently. This allows the effectiveness of traditional medicine to be determined either within its own theoretical framework or within that of conventional medicine.

**Ethnographic design**
Ethnographic studies that document the social and cultural context in which a traditional practice emanates may be appropriate in situations where there is no available scientific literature or other documentation. These and other qualitative studies can provide baseline information from which hypothesis may be generated, and can lead to further research.

**Observational design**

Observational studies collect findings on a therapeutic or prophylactic treatment under routine conditions. The special feature of these studies is that they seek as far as possible, not to influence the individual doctor-patient relationship with respect to indications, and the selection of and carrying out the treatment. These studies may be conducted with or without a control group. The specific details of the study (e.g. the time and extent of examination for each individual patient, the number of patients involved) and the envisaged methods (e.g. data recording and evaluation) must be adapted to the question investigated in the study (e.g. safety or appropriate posology). Observational studies have specific advantages in studying aspects of clinical safety. The use of such studies to prove efficacy is limited because bias in patient selection may occur. Nevertheless, the level of evidence on efficacy of traditional medicine can be significantly increased by well-designed observational studies.

**Study outcome measures**

It is essential that the outcome measures chosen be appropriate to the research question. Appropriate outcomes may include quantitative and qualitative outcomes; primary and/or secondary outcomes, and generic and/or
highly specific outcomes.

**Selection of patients (WHO guidelines, 2000)**

It is essential that the sample represent the target population of patients to which the results would be generalized. Publication of the study requires a clear description of the patients using both traditional and conventional terms. The reliability of the categorization/diagnostic criteria used in the study should be considered and stated. The source of the patients under study should be comprehensively described along with details of the recruitment process. The inclusion and exclusion criteria should be completely described and rationalized. Any potential bias in patient selection, recruitment and enrolment should be excluded. Investigators should be aware of any potential errors that may occur when studying traditional medicine out of context and without reference to its traditional theories and concepts.

When the research involves techniques that depend on skills that may differ between practitioners, such research should be conducted by more than one practitioner in order to increase the generalizability of the results.

**Sample size**

The number of patients in a study needs to be adequate, in order to be able to determine any clinically important difference between the study groups. With respect to the study design, the statistical methods used should be appropriate to the proposed analysis of the study's outcome.
Control groups

A well-conducted and controlled clinical trial could provide sufficient evidence to establish a relationship between the use of a herbal medicine or traditional procedure-based therapy and the prevention, diagnosis, improvement or treatment of an illness, provided there is a supporting body of evidence from observational or mechanistic studies.

Randomized controlled trials require one or more control groups for purposes of comparison. The selection of control groups depends on the objectives of the study. In the evaluation of traditional medicine, a concurrent control group should be used. The control groups may involve:

- well established treatment
- non-treatment
- different doses of the same treatment
- sham or placebo treatment
- full-scale treatment
- minimal treatment
- alternative treatment

Different controls can be used in clinical trials to answer different questions. The use of a placebo, when possible, is desirable, because it generates evidence of better quality. Placebo-controlled trials are intended to establish whether treatment is valuable over and above what might be achieved by a control treatment, and not whether treatment is valuable at all. Thus, it allows researchers to distinguish specific from non-specific effects of treatment.
in order to determine whether the additional cost, risk and effort of a specific treatment are worthwhile. It is also important for understanding the mechanism of a treatment. This is true for the evaluation of all drugs. It is not only of academic interest, but it also of practical value, especially for developing new treatments from traditional ones. However, in some cases, placebo-controlled trials may not be possible.

It is preferable to compare a herbal medicine with both a well-established treatment and another control group to determine whether the herbal medicine is useful in the context of current best practices.

One specific problem in clinical research of traditional medicine is the simultaneous conventional treatment of patients in a study. It may not be ethically possible to withdraw the conventional treatment. Therefore, in such cases, the focus of research may be on the additional or supportive effects of traditional medicine. Research on combinations of traditional and conventional medicine should always consider potential therapeutic interactions and side-effects.

**Randomization**

Randomization has been a tremendous advance in developing comparable groups to assess therapeutic interventions. It is essential to control various known, and even unknown, biases. Nevertheless, there are many situations where randomization can be impossible for unethical. The best way to solve this problem is probably by the proper selection of control treatments.
Blinding in clinical trials

Blind assessment is a critical component of conventional evaluation of therapeutic interventions. However, in the evaluation of efficacy of traditional procedure-based therapies (such as physical therapy, surgery, acupuncture and manual therapy), it can be difficult, impractical or impossible for the practitioner to be kept ignorant of what treatment the patients are receiving. It is essential that this be noted in the evaluation of the validity of a study and that the judgement on its validity be applied consistently across all systems of conventional and traditional medicine.

Treatment blinding in the evaluation of herbal medicines should adopt the approach of conventional medicines, e.g. using active and control formulations with similar colour, taste and weight. However, if the herbal medicine can not be administered in a predetermined standardized formulation, it will be impossible to keep the treatment blinded. Treatment blinding is also difficult to implement in most types of traditional procedure-based therapies. It is important, however, to reduce any bias introduced by non-blinded treatment by carrying out a blinded assessment of the primary outcomes of the study.

INTRODUCTION TO SIDDHA PREPARATIONS

Introduction to the siddha system of medicine

This principles and doctrines of this system, both fundamental and applied, have a close similarity to Ayurveda, with specialization in Iatro-chemistry. According to this system the human body is the replica of the universe and so are the food and drugs irrespective of their origin.
Like Ayurveda, this system believes that all objects in the universe including human body are composed of five basic elements namely, earth, water, fire, air and sky. The food, which the human body takes and the drugs it uses are all, made of these five elements. The proportion of the elements present in the drugs vary and their preponderance or otherwise is responsible for certain actions and therapeutic results.

As in Ayurveda, this system also considers the human body as a conglomeration of three humours, seven basic tissues and the waste products of the body such as faeces, urine and sweat. The food is considered to be basic building material of human body which gets processed into humours, body tissues and waste products. The equilibrium of humours is considered as health and its disturbance or imbalance leads to disease or sickness.

This system also deals with the concept of salvation in life. The exponents of this system consider achievement of this state is possible by medicines and meditation.

**Formulations in siddha system (Ayush database, 2005)**

The system has developed a rich and unique treasure of drug knowledge in which use of metals and minerals is very much advocated. Some idea about the depth of knowledge the system possesses in the field of mineral, materia medica can be formed from the detailed drug classification, briefly described below:
There are 25 varieties of water-soluble inorganic compounds called ‘UPPU’. These are different types of alkalies and salts.

There are 64 varieties of mineral drugs that do not dissolve in water but emit, vapours when put in fire. Thirty-two of these are natural and remaining are artificial.

There are seven drugs that do not dissolve in water but emit vapour on heating.

The system has classified separately classes of metals and alloys, which melt when, heated and solidifies on cooling. These include items like gold, silver, copper, tin, lead and iron. These are incinerated by special processes and used in medicine.

There is a group of drugs that exhibit sublimation on heating and includes mercury and its different forms like red sulphide of mercury, mercuric chloride and red oxide of mercury etc.

Sulphur, which is insoluble in water, finds a crucial place in Siddha materia medica along with mercury for use in therapeutics and in maintenance of health.

The above classification shows detailed knowledge and study of minerals that this system has evolved for treatment. In addition there are drugs obtained from animal sources.
Chemistry in Siddha

In Siddha system chemistry had been found well developed into a science auxillary to medicine and alchemy. It was found useful in the preparation of medicine as well as in transmutation of basic metals into gold. The knowledge of plants and mineral were of very high order and they were fully acquainted with almost all the branches of science. The Siddhars were also aware of several alchemical operations divided into several processes such as – calcinations, sublimation, distillation, fusion, separation conjunction or combination, congelation, cibation, fermentation, exaltation i.e. the action or process of refining gold, fixation i.e. bringing to the condition of being non-volatile i.e. to the state of resisting the action of fire, purification, incineration of metals, liquifaction, extraction and so on.

Even cupellation of gold and silver which is an essential process in Alchemy in which is claimed to have been discovered by the Arabs, was known to the Siddhars long long before.

They were even polypharmacists and as such were engaged in boiling, dissolving, precipitating and coagulating chemical substances. Some of their secret methods, especially those in fixing and consolidating certain volatile substances that could not resist the action of fire, such as Mercury, Sulphur, Orpiment, Vermilion, Arsenic etc. continue still a mystery.
Introduction to siddha preparations – Uchidums and Parpams (formulary of Siddha medicines, 1993; Gunapadam, 1979)

Uchidum

Uchidum are herbal preparations of siddha system which would be prepared by process of powdering, mixing and steaming the herbal ingredients and administered by making into a paste with the vehicle specified.

Ex :- Vizhudu Uchidum, Atti Uchidum, Samai Uchidum etc.

Parpams

Parpams are herbo-mineral preparations of siddha system, which was equivalent to that of bhasmas of Ayurvedic system. It was prepared by alchemical process such as calcinations, recalcination and fusion techniques.

Clinical studies on herbal and herbo-mineral antidiabetic preparations

A literature review of traditional formulations screened for antidiabetic activity in human volunteers revealed that six specific herbal and hero-mineral formulations have been studied in patients with type 2 diabetes.

Studies were reported for three Ayurveda (D-400, MA-471 and Ayush-82 (Pandey et al 1995; Sircar et al., 1996) and three from Siddha formulations (Abraga Chendooram, Sandanapoddi (Shankar and Singhal, 1994) and Kadal Azhinjil (Kumar et al, 1999) and these formulations have been evaluated by randomized open label prospective cohort studies and these formulations showed significant antidiabetic activity.