1. INTRODUCTION

1.1 GENERAL INTRODUCTION

The Siddha medicine is one of the oldest medical systems known to mankind. Contemporary Tamizh literature mentions the origin of the medical system from Southern India in the state Tamil Nadu, as part of the trio Indian medicines - Ayurveda, Siddha and Unani. Reported to have surfaced more than 2500 years ago, the Siddha system of medicine is considered one of the most antiquated traditional medical systems. The Siddha Science is the oldest traditional treatment system generated from Dravidian culture. The Siddha System of medicine flourished in the period of Indus Valley Civilization. Palm Leaf Manuscripts says that Siddha System was first described by Lord Shiva to his wife Parvathy. Parvathy explained all this knowledge to her son Lord Muruga. He taught all these knowledge to his Disciple Sage Agasthya. Agasthya taught 18 Siddhars and they spread this knowledge to human beings.

The word Siddha comes from the word Siddhi which means an object to be attained perfection or heavenly bliss. Siddha is focused to "Ashtamahasiddhi" that is the eight supernatural powers. Those who attained or achieved the above said powers are known as Siddhars. There were 18 important Siddhars in olden days and they developed this system of medicine. Hence, it is called Siddha Medicine. The Siddhars wrote their knowledge in palm leaf manuscripts, fragments of which were found in different parts of South India. It is believed that some families may possess more fragments, but keep them solely for their own use. There is a huge collection of Siddha Manuscripts kept by Traditional Siddha Families.
According to the experts, there were 18 principal siddhars. Of these 18, Agasthya is believed to be the father of siddha medicine. Siddhars were of the concept that a healthy soul can only be developed through a healthy body. So they developed methods and medication that are believed to strengthen their physical body and thereby their souls. Men and women who dedicated their lives into developing the system were also called Siddhars. They practiced intense yogic practices, including years of periodic fasting and meditation and were believed to have achieved supernatural powers and gained the supreme wisdom and overall immortality. Through this spiritually attained supreme knowledge, they wrote scriptures on all aspects of life, from arts to science and truth of life to miracle cure for diseases.

"Siddha medicine" means medicine that is perfect. Siddha medicine is claimed to revitalize and rejuvenate dysfunctional organs that cause the disease and to maintain the ratio of vata, pitta and kapha. The Siddha medicine given by practitioners includes leaves, flowers, fruit and various roots in a mixed basis. In some extraordinary cases, when the disease is not cured, they recommend metallic preparation like Thanga Pashpam (gold). Most of the practicing Siddha medical practitioners are traditionally trained, usually in families and also by different gurus (teachers). When the guru is also a martial arts teacher, he is also known as an ashan. They make a diagnosis after a patient's visit and set about to refer to their manuscripts for the appropriate remedies, which a true blue physician compounds by himself or herself, from thousands of herbal and herbo-mineral resources. The methodology of Siddha thought has helped decipher many causes of disorders and the formulation of curious polyherbal remedies which may sometimes have more than 250 ingredients, have cured many diseases.
1.2 HERBAL FORMULATION

World Health Organization (WHO) has defined herbal medicines as finished labeled medicinal product that contain active ingredients, aerial or underground parts of the plant or other plant material or combinations.

**Poly herbal formulations**

Formulations which contain two or more herbal drugs with multiple pharmacological action therapeutic effect are called as poly herbal formulation. It contains more than two herbal drugs and every drug has number of the chemical constituents, hence poly herbal formulation contains a huge number of these phytochemical constituents\(^5\).

Herbal formulations have reached widespread acceptability as therapeutic agents for diabetics, arthritis, liver diseases, cough remedies and memory enhancers\(^6\). Owing to the medicinal properties attributed to a crude drug, it is necessary to maintain its quality and purity in commercial market. It is, however that the drugs in commerce are frequently adulterated and do not comply with the standards prescribed for authentic drug\(^7\). Most of the traditional systems of medicine are effective but they lack standardization. So, there is a need to develop a standardization technique. Central Council of Research in Ayurveda and Siddha has given preliminary guidelines for standardizing these conventional formulations. For the uniformity of batches in production of herbal formulations it is necessary to develop methods for evaluation. Standardization of drugs means confirmation of its identity and determination of its quality and purity. Initially the crude drugs were identified by comparison only with the standard description available. At present due to advancement in the chemical knowledge of crude drugs various methods like
botanical, chemical, spectroscopic and biological methods are used for estimating active constituents present in the crude drugs in addition to its physical constants.\(^8\)

**Market Importance and Uses of Herbal Medicine in India**

Medicinal plants are important for pharmacological research and drug development, not only when plant constituents are used directly as therapeutic agents, but also as starting materials for the synthesis of drugs or as models for pharmacologically active compounds. Regulation of exploitation and exportation is therefore essential, together with international cooperation and coordination for their conservation so as to ensure their availability for the future better utilization of these complementary systems of medicine. In India, there are currently about 250,000 registered medical practitioners of the Ayurvedic system (total for all traditional systems: approximately 291,000), as compared to about 700,000 of the modern medical system. In every Indian state, about one-third of the government medical posts are occupied by physicians who belong to the traditional systems.\(^9\)

**Contaminants in herbal medicine**

Potential contaminants of herbal medicines include microorganisms, microbial toxins, pesticides; fumigation agents, radioactivity, and the presence of toxic compounds of toxic metals. Some of these contaminants have been identified by the Committee for Proprietary Medicinal Products (CPMP) of the European Community (EC) for use in controlling the purity of herbal medications in the European Union (EU). The CPMP Guidelines highlight the need for good control of starting materials and the finished product and emphasize the importance of good manufacturing practice.\(^{10-11}\)
1.3 STANDARDIZATION OF HERBAL FORMULATIONS

Standardization means analyzing the amount and potency of active ingredients believed to be present in each herb claimed in the formulation.

Need for Standardization

In recent years there is a spurt in the interest regarding survival of Ayurvedic forms of medication. In the global perspective, there is a shift towards the use of medicine of herbal origin, as the dangers and the short coming of modern medicine have started getting more apparent and as majority of Ayurvedic formulations are prepared from herbs.

It is the cardinal responsibility of the regulatory authorities to ensure that the consumers get finished products in pharmacopoeias controlling the manufacturing through the use of formularies and the medication, with guaranteed purity, safety, potency and efficacy. This duty is discharged by regulatory authorities by rigidily following various standards of quality prescribed for raw materials and monitoring the manufacturing operation through statutory imposed “Good Manufacturing Practices”.

Herbal products have been enjoying renaissance among the customers throughout the world. The quality of herbal medicine i.e., the profile of the constituents in the final product has implication in efficacy and safety. Due to complex nature and inherent variability of the constituents of the plant based drugs, it is difficult to establish quality control parameter and modern analytical technique are expected to help in circumventing this problem.

The quality control of crude drugs and herbal formulations is of paramount importance in justifying their acceptability in modern system of medicine. But one of
the major problems faced by herbal drug industry is non-availability of rigid quality control profile for herbal material and their formulations.

The task of lying down standard for quality control of herbal drugs and their formulations involves biological evaluation for particular disease area, chemical profiling of the material and lying down specification for the finished product. Therefore, in case of herbal drugs and product, the word “standardization” should encompass entire field of study from cultivation of medicinal plant to its clinical applications.

Plant material and herbal remedies derived from them represent substantial portion of global market and in this respect internationally recognized guidelines for their quality control are necessary. WHO has emphasized the need to ensure quality control of medicinal plant products by using modern technique and by applying suitable parameters and standards. In order to overcome certain inevitable shortcoming of the Pharmacopoeial monograph other quality control measures must be explored\textsuperscript{12-14}.

1.4 DIABETES MELLITUS

Diabetes mellitus is a complex metabolic disorder resulting from either insulin insufficiency or insulin dysfunction. Type I diabetes (insulin dependent) is caused due to insulin insufficiency because of lack of functional beta-cells. Patients suffering from this are therefore totally dependent on exogenous source of insulin while patients suffering from Type II diabetes are unable to respond to insulin and can be treated with dietary changes, exercise and medication. 346 million people worldwide have diabetes. In 2004, an estimated 3.4 million people died from consequences of high blood sugar. More than 80% of diabetes deaths occur in low
Introduction

and middle income countries. WHO projects that diabetes death will double between 2005 and 2030.

Healthy diet, regular physical activity, maintaining a normal body weight and avoiding tobacco use can prevent or delay the onset of type-2 diabetes. Over time, diabetes can damage the heart, blood vessels, eyes, kidneys and nerves.

Diabetes increases the risk of heart disease and stroke. 50% of people with diabetes die of cardiovascular disease (primarily heart disease and stroke). Combined with reduced blood flow, neuropathy in the foot increases the chance of foot ulcers and eventual limb amputation. Diabetic retinopathy is an important cause of blindness and occurs as result of long-term accumulated damage to the small blood vessels in the retina. After 15 years of diabetes, approximately 2% of people become blind and about 10% develop severe visual impairment. Diabetes is among the leading causes of kidney failure. 10-20% of people with diabetes die of kidney failure.\textsuperscript{15}

Wide arrays of plant derived active principles representing numerous phytochemicals have demonstrated consistent hypoglycaemic activity and their possible use in the treatment of diabetes mellitus\textsuperscript{16}. In the traditional system of Indian medicine combined extracts of plants are used as drug of choice rather than individual & Many of these have shown promising effects\textsuperscript{17}.

1.4.1 Types of Diabetes mellitus:

According to modern concept:

Diabetes is of three types\textsuperscript{18}:

1. **Type 1 or Insulin Dependent Diabetes Mellitus:** Known as Juvenile diabetes Mellitus. 5-10% cases are diagnosed as Type 1. It is an autoimmune disorder when the immune system goes against its own self causing
destruction of the pancreatic cells that produce insulin. Seen usually in children. Increased urination, increased thirst, weight loss are usually seen. No family history generally present. Insulin shots are given usually in modern medicine.

2. **Type 2 or Non Insulin Dependent Diabetes Mellitus**: Most common type. Slow onset with symptoms like increased thirst, increased urination and weight loss. Usually these people are obese with sedentary life style and a strong family history. Due to ineffective glucose metabolism, the body uses alternatives like fat metabolism to produce energy leaving the person tired and fatigue seen.

3. **Gestational Diabetes**: Seen during pregnancy. About 3-5% ladies have chances to develop Gestational diabetes. This happens when the body does not make enough insulin or resist direct action of insulin due to hormones. These patients have 40% chances of developing Type 2 Diabetes if they are obese or have irregular food habits. Diet management alone manages this condition well. Insulin is sometimes given.

1.4.2 **Symptoms of Diabetes mellitus**:¹⁹

- **Polydipsia (Increased thirst)**: The concentration of glucose in blood makes the brain send signals for dilution of blood hence one feel the urge to drink more water

- **Polyphagia (Increased appetite)**: Insulin also responsible for hunger, increase insulin level stimulates hunger and desire to eat more

- **Polyurea (Increased Urine output)**: Body tries to get rid of increased blood sugar and thus increased urine is seen to eliminate the extra glucose from the body making the sufferer dehydrated and tired.
• **Weight fluctuation:** Earlier seen as weight loss due to utilization of fat from body for energy, later weight gain occurs due to increased appetite.

• **Blurred vision**

• **Irritability**

• **Infections:** UTI and Skin infections seen usually

**Poor wound Healing:** Increased blood glucose inhibits WBC responsible for immunity of the body, delays the healing power.

**Complications:** Untreated Diabetes may lead to irreversible damage to the Eyes (Retinopathy), Kidneys (Nephropathy), Nerves (Neuropathy), Heart (Heart Attack) and Feet (Diabetic Foot).

### 1.4.3 Managing Diabetes Mellitus

Both Type 1 and Type 2 Diabetes can be managed through diet, Exercise, Routine check up and Medicines.

**Diet:** A balanced diet with veggies, fruits, whole grain, beans, fish, lean mean meat, non fat dairy, and fiber rich food like salad is suggested. Frequent and a portion meal is the best. It is myth that diabetics have to cut off sugar completely. One can take sugar and curb in permissible limits.

**Exercise:** Exercise increases the blood sensitivity to insulin stimulates muscle to use glucose. 15 minutes before exercise, diabetes should have some snacks or fruits else the sugar may dip making him/her hypoglycemic.

**Routine Check up:** Record of sugar level and plan of diet accordingly will be useful for management of diabetes mellitus.

The following table 1 depicts the non-insulin agents available for the treatment of diabetes mellitus.
1.4.4 Management of Diabetes mellitus in modern medicine, its advantages and disadvantages\textsuperscript{21}

![Table 1 - Non-insulin agents available for treatment of diabetes]

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Route of administration</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biguanides ( [\text{metformin}] )</td>
<td>Oral</td>
<td>Effectively lowers ( \text{HbA}_{1c} ) \text{, low cost, does not cause weight gain}</td>
<td>GI complaints, minimal risk of lactic acidosis (contraindicated in patients older than 80 y and in those with elevated creatinine levels)</td>
</tr>
<tr>
<td>Sulfonylureas ( [\text{tolbutamide, glyburide, gliazide, glimepiride}] )</td>
<td>Oral</td>
<td>Available as generics ( \text{(low cost)} )</td>
<td>Can cause weight gain</td>
</tr>
<tr>
<td>Disaccharidease inhibitors ( [\text{acarbose, miglitol}] )</td>
<td>Oral</td>
<td>Do not promote weight gain; safe in patients with renal failure; reinforce carbohydrate restriction through adverse response</td>
<td>Flatulence, abdominal discomfort, diarrhea, relatively high cost</td>
</tr>
<tr>
<td>Thiazolidinediones ( [\text{rosiglitazone, pioglitazone}] )</td>
<td>Oral</td>
<td>May preserve beta cells from ongoing destruction</td>
<td>Cause fluid retention ( \text{(sometimes leading to heart failure)} ); stimulate accumulation of adipose tissue</td>
</tr>
<tr>
<td>Meglitinides ( [\text{repaglinide, nateglinide}] )</td>
<td>Oral</td>
<td>Rapid disappearance time results in lower risk of hypoglycemia than with sulfonylureas</td>
<td>Much shorter duration of action than sulfonylureas; thus, these agents must be taken before meals; moderately high cost</td>
</tr>
<tr>
<td>GLP analogs ( [\text{exenatide}] )</td>
<td>Parenteral</td>
<td>May result in progressive weight loss in some patients</td>
<td>Nausea ( \text{(often severe); must be injected twice daily; high cost} )</td>
</tr>
<tr>
<td>Amylin analogs ( [\text{pramlintide}] )</td>
<td>Parenteral</td>
<td>Weight loss can occur</td>
<td>Nausea; unpredictable hypoglycemia; high cost</td>
</tr>
<tr>
<td>DPP-IV inhibitors ( [\text{sitagliptin}] )</td>
<td>Oral</td>
<td>No prominent side effects, low risk of hypoglycemia</td>
<td>Does not lead to weight loss; high cost</td>
</tr>
</tbody>
</table>

\( \text{HbA}_{1c}, \text{glycosylated hemoglobin; GLP, glucagon-like peptide; DPP-IV, dipeptidyl peptidase IV} \)

1.4.5 Management of Diabetes mellitus by the Siddha system of medicine

Diabetes mellitus is a condition which can be compared with \textit{Neerizhivu} in Siddha. The other names described in the texts are the \textit{Madhumegham} and \textit{Inippuneer}. The signs and symptoms explained is increased urination both in frequency and quantity, there will be flies surrounding the urine voided place, weight loss, dryness of the skin, etc.
1.4.6 Herbs and Herbal formulation used in Siddha system of medicines for the management of Diabetes mellitus

In Siddha, the management of a disease not only depends on the medicine but the modification of food, habits and lifestyle also. There are several antidiabetic medicine described in the literatures and practiced successfully by Siddha practitioners. The regulations in food, daily habits etc., are the speciality of this system. Some commonly used medicines are

1. Madhumehga chooranam
2. Seenthil chooranam
3. Naval chooranam
4. Seenthil kudineer
5. Aavarai kudineer
6. Abraga parpam
7. Vanga parpam. etc.,

In addition to the prepared medicines there are several herbal combinations said in the texts for the management of diabetes mellitus. All these medicines are to be used with the prescription of a siddha medical practitioner and with proper regimen. These medicines include several plants with anti-diabetic property like,

Jambulinor naval (Syzygium cumini Fam: Myrtaceae)
Sarakarai Kolli (Gymnema sylvestre Fam: Asclepidaceae)
Kadalazhinjil (Salacia chinensis Fam: Hippocrateaceae; Celastraceae)
Seenthil or Amrithu (Tinospora cordifolia Fam: Menispermaceae)
Vilwam (Aegle marmelos Fam: Rutaceae) etc. 22.
1.5 SIDHHA KUDINEER FORMULATION

Siddha systems of medicines are more effective to control the type-2 diabetes. Siddha Pharmacopoeia describes 32 types of internal medicines, of which Kudineer is one of the most important polyherbal formulations equally referred to as khashayas in Ayurveda. These are more useful to prevent diabetes and associated complications.

Some important kudineer formulations

1. Formula 1-Aavarai ilai kudineer

2. Formula 2-Aavarai thulir kudineer
Composition: Aavarai thulir-1 Part, Kal madam-1Part, Kondrai ver -1Part.

3. Formula 3-Vilva ilai kudineer
Composition: Nalla vellam-1Part, Thanneer-1Part, Vilva ilai-1Part, Vilva pattai -1Part

4. Formula 4- Vilaver kudineer
Composition: Vilaver -1Part, Aavarai ver -1Part, Varat pool aver -1Part, Ilanthai ver pattai -1Part, Kattu malli ver-1Part

Formula 5-Thetran kottai kudineer
1.5.1 SWOT ANALYSIS OF KUDINEER FORMULATION

Strength - Official, traditional, reputed formulation.

Weakness - Lack of standardization to meet the global standards

Opportunities- Development of scientific evidence may strengthen the use of this formulation.

Threatens- Lot of patient’s compliance to use this formulation as search

Thus the current study has been undertaken to choose the clinically proven, cost effective, official, traditional kudineer formulation to study scientifically to develop Pharmacopoeial standards for the benefit of mankind.