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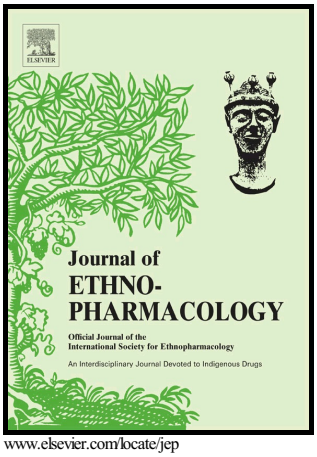

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Plants used to treat diabetes in Sri Lankan Siddha Medicine – an ethnopharmacological review of historical and modern sources

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Abstract

Introduction and background:

In recent decades diabetes mellitus has become a considerable health problem in countries like Sri Lanka and results in an increasing economic burden hampering the social and economic development of these countries. About 60 to 70 % of the rural population in Sri Lanka rely on indigenous medicinal systems as their main source for primary health care. Siddha (Tamil) Medicine is one of the four Sri Lankan traditional medicinal systems and it is practised mostly in the eastern and northern provinces of Sri Lanka where the majority of Tamils reside.

Aim:

The foundation of this study is a documentation of plant species recorded in historical and modern Sri Lankan Siddha Medical documents used to treat diabetes. Based on the systematic documentation and analysis of Siddha concepts about diabetes and its signs and preparations used to treat diabetes in Sri Lankan Siddha Medicine, the plant species included in these preparations (excluding globally or very widely used, very well studied species) were evaluated in terms of the current state-of-the-art about these species' pharmacology and effectiveness in order to lay a foundation for their further development.

Method:

Historic and modern Sri Lankan university texts books in Tamil were used as sources for information on diabetes Siddha concepts and antidiabetic Sri Lankan Siddha Medicine preparations. Information on the known antidiabetic effects of extracts and compounds obtained from these species were used in order to assess the current state of the art of these species.

Results and discussion:

Information of ingredients, preparation methods, amount of ingredients used, and dosages of 60 antidiabetic Sri Lankan Siddha Medicine preparations were obtained. Animal parts including marine organisms, inorganic substances, and plants are the three types of ingredients used. Overall 171 plant species in 73 families were documented. *Senna auriculata* (L.) Roxb. (Fabaceae) was identified as the most frequently cited species. Globally distributed and very well studied plants were excluded in the pharmacological and clinical literature review which includes 123 plant species. The majority (48 %) of the plant species reviewed were studied up to *in vivo* level as the current maximum level of scientific evidence available. Followed by 41 % of species have not been studied for antidiabetic activities or did not show

antidiabetic activity. Moreover, 6 % and 5 % were studied up to *in vitro* and in clinical levels, respectively. The majority of the species were studied only in the models that represent type 1 diabetes.

Conclusion:

This is the first study systematically assessing the importance of preparations and plants used in antidiabetic Sri Lankan Siddha Medicine preparations. Antidiabetic plants are a crucial health care resource in Sri Lankan Siddha Medicine. This study also identified a wide range of methodological problems in the studies conducted so far. More and better type 2 diabetes models should be employed in future studies. This comprehensive review creates the basis for a more systematic study of these local resources.

List of abbreviations

DM, diabetes mellitus; SM, Siddha Medicine; SL, Sri Lanka; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus

Keywords: Alpha glucosidase inhibition assay, alpha amylase inhibition assay, Diabetes Mellitus, Fabaceae, *Senna auriculata*, Siddha Medicine, Sri Lanka, Streptozotocin, Tamil Medicine

1. Introduction

Diabetes mellitus (DM) has become an enormous and fast developing health problem and is an increasing economic burden hampering the social and economic development of many countries. Undiagnosed cases cause greater risk of elevating cost and dangerous complications (IDF, 2014). In 2015, globally 415 million (215.2 million men and 199.5 million women) people had DM with a prevalence of 8.8 %. In other words, one in eleven people have DM (IDF, 2015). Nearly 90 % of people with DM around the world have type 2 DM (T2DM) (WHO, 1999) and in every country the number of people with T2DM has been increasing mostly dramatically (IDF, 2014). The majority of people with DM live in urban areas (269.7 million; with 145.1 million in rural areas). In China alone there are 109.6 million cases (IDF, 2015). Moreover, the majority (320.5 million) of people with DM are in the 20 – 64 age range. In 2015, 5 million DM related deaths were reported and there were an estimated 192.8 million undiagnosed cases (46.5 %). The highest proportion of undiagnosed cases are found in Africa (66.7 %) (IDF, 2015). Every six seconds one person dies from DM. Importantly, 77 % of the diabetics live in low and middle income countries, and thus have a much more limited access to biomedical health care (IDF, 2014).

In 2015, globally US$ 673 billion (12 % of health expenditure) was spent on treating DM whereas the USA is the country with the highest costs (US$ 320 billion) (IDF, 2015). Europe has the highest prevalence of children with T1DM. For 2040, it is estimated that 642 million people will have DM representing a global DM prevalence of 10.4 %.

In South Asia (Bangladesh, Bhutan, India, Maldives, Nepal, and Sri Lanka (SL)) and Mauritius, in 2015 there were 78 million diabetics and by 2040 this will increase to

140 million (IDF, 2015). One in twelve people in this region has DM (IDF, 2014). Again, in 2015 there were 40.8 million undiagnosed cases and DM caused 1.2 million deaths in South Asia and Mauritius area. Some 53 % of those deaths were in people under 60 years old. More women (664,071) died than men (524,394) with DM, whereas majority of people with DM died in India in this region. The largest number of diabetics (20 to 79 years) in South Asia and Mauritius area lives in India (69 million).

In SL, in 2015 there were 1.2 million diabetics including 625,000 undiagnosed cases (20 to 79 years) (IDF, 2015). One in twelve people had DM (IDF, 2014). In 2015, 16,318 deaths (20 to 79 years) were caused by DM. The cost per diabetic is US$ 429.2 (IDF, 2015). Overall, there is a need to develop national and regional strategies to prevent the development of DM and to mitigate its effects (Home et al., 2013).

1.1. Plants, traditional medicines, and diabetes - globally

Plants have been used in traditional medicines to treat vast number of disorders including DM for centuries and these are easily available and affordable (Nearing, 1985). Traditional Medicine preparations could be a potential source of novel antidiabetic compounds (Marles and Farnsworth, 1995) or phytomedicines / supplements. Metformin (a biguanide) is a primary line drug currently used to control DM in Biomedicine which was developed from galegine (a guanidine) isolated from *Galega officinalis* L. (Fabaceae) (Witters, 2001).

In recent years systematic studies and comparative reviews have been published highlighting the importance of antidiabetic plants in countries, like India (Grover and Yadav, 2002), Nigeria (Ezuruike and Prieto, 2014), and Mexico (Andrade-Cetto and Heinrich, 2005). In the USA 22 % of people with DM use herbal therapy and 31 % use dietary supplements (Shane-McWhorter, 2009).

1.2. Plants, traditional medicines, and diabetes - in Sri Lanka

About 60 to 70 % of the rural population in SL use indigenous medicinal systems as their main source for primary health care (Perera P.K., 2012). Siddha (Tamil) Medicine (SM) is one of the four traditional medicinal systems currently practised in SL (Weragoda, 1980) and it is practised mostly in the east and north provinces of SL where the majority of Tamils reside (Sivashanmugarajah, 2000). People with DM very commonly use herbal supplements in SL (Medagama et al., 2014). A review of plants used to treat DM in SL by Ediriweera and Ratnasooriya (2009) only includes information collected from Ayurvedic and traditional physicians in south, west, and Sabaragamuva provinces of SL, where SM is not practised. Only a few ethnobotanical surveys and clinical studies of SM preparations have been carried out in SL. Recent ethnobotany surveys in Sillalai, Jaffna (Rajamanoharan, 2013) and Asikulam, Vavuniya (Rajamanoharan, 2014) revealed that medicinal plants are mostly used to treat disorders including DM. Arugankattai (அறுகங்கட்டை) (Gly-Cyn-Neu), literally *Glycyrrhiza glabra* L. and *Cynodon dactylon* (L.) Pers. for neuropathy, is a topical, two component Siddha preparation used to treat neuropathy. Recent clinical studies of topically administering Arungankattai to people with DM for 4 weeks showed effective improvements in in diabetic complications without any side effects (Rajamanoharan and Sewwandi, 2013). However, no detailed review of plants used in Sri Lankan SM is available. Recently a book written in Tamil, "A handbook of herbs

for healthy life" (மூலிகைகளும் ஆரோக்கிய வாழ்வும் பற்றிய கைநூல் - Moolihaihalum Aarokkiya Vaalvum Patiya Kainool) (Rajamanoharan and Sivathas, 2014) provides a description of herbs and practical advice to prevent and treat several simple disorders at home focusing on the needs of rural Tamil populations around the world. The search for novel AD medications from Indian Traditional Medicine (Marles and Farnsworth, 1995) continues and since SM has not been studied in any great detail, it offers unique opportunities.

2. Aim

With a lack of critical appraisal of medicinal plans used in SM in the treatment and management of DM, this review aims at:

- Presenting a comprehensive review of DM in SM including the indigenous concepts about its symptoms.
- Reviewing information on local and traditional uses of antidiabetic SL SM preparations as they are recorded in historical and modern documents.
- Assessing the reported scientific evidence for the effectiveness of the plants used in those preparations.

3. Background and methods

3.1. Diabetes mellitus

DM's symptoms are well known including hyperglycemia with a wide range of complications (Singh et al., 2014) including damage to the nervous system, blood vessels, eyes, gums and teeth, heart, kidneys, or feet and skin (Zaccardi et al., 2015). Three groups are distinguished: (1) Autoimmune T1DM or insulin dependent DM or juvenile DM (2) T2DM or noninsulin dependent DM or Maturity Onset DM and (3) Gestational DM. All forms of DM are treated by dietary control. However, T1DM requires insulin replacement via injection of hormone or Islet transplantation. Novel delivery via oral, inhaled and sublingual routes are the topic of intense current investigation (Shahani and Shahani, 2015). T2DM is considerably more amenable to therapeutic drug intervention and is treated with insulin secretagogues e.g. sulphonylureas, megltinides, incretins; insulin sensitisers e.g. thiazelidendiones, metformin; direct reduction of plasma glucose e.g. SGLT2 inhibitors, metformin (Bailey et al., 2016) and there are a wide range of preventive interventions under development (Breeze et al., 2015). Natural products and herbal medicines that have claimed to be effective in the treatment of DM are thus most effective in the treatment of T2DM (Kouzi et al., 2016). As discussed earlier this is fortunate as T2DM is the form of DM that makes up the major part of the global epidemic.

3.2. Bioassays and *in vivo* models used for studying andtiiabetic activity

Diverse models have been employed to investigate antidiabetic effects of Siddha medicinal plants. Pharmacodynamic models include *in vitro* bioassays*, in vivo* and clinical models and their relevance with regards to assessing the antidiabetic effects of SM vary. There are a large number of targets and bioassays used for T2DM. In

ethnopharmacology studies the following bioassays and *in vivo* models are particularly widely used.

3.2.1. *In vitro* bioassays

α-glucosidase and α-amylase inhibition assays are commonly employed to investigate anti-diabetic activity in *in vitro* studies. Bioassays such as Acetyl CoA carboxylase 1 enzyme bioassay and Acetyl CoA carboxylase 2 enzyme bioassay which are closely related in developing T2DM (Munday, 2002). Currently α-glucosidase inhibitors such as acarbose and miglitol are prescribed in Biomedicine. However, they cause unwanted adverse side effects such as abdominal pain, diarrhoea, bloating, and passing of gas (TASHSP, 2016a; 2016b).
The advantages of *in vitro* bioassays are economic, less time consuming, and more samples can be screened. However, a major disadvantage is that anti-diabetic activity against a single target can only be tested in each bioassay rather than general anti-diabetic activity against the pathological phenotype.

3.2.2. *In vivo* models

In vivo anti-diabetic activity is studied in T1DM and type T2DM animal models typically rat and mouse. The advantage of these studies is that one can observe therapeutic effects on physiology, although one might not know the true drug target that achieves that effect.

3.2.3. Type 1 diabetes animal models

In T1DM, β cells in pancreas are destroyed and do not secrete adequate insulin. Streptozotocin and Alloxan induced diabetic animal models are commonly used to investigate T1DM (King and Bowe, 2016; King, 2012). Streptozotocin [2-deoxy-2-(3-(methyl-3-nitrosoureido)–D-glucopyranose] and Alloxan (2,4,5,6-tetraoxypyrimidine; 5,6-dioxyuracil) both are toxic to β cells in pancreas and destroy them (Szkudelski, 2001). However, constant and everlasting DM conditions can be obtained in streptozotocin induced diabetic models. On the other hand, both Alloxan and Streptozotocin induced diabetic *in vivo* models are not identical to human diabetic conditions (Islas-Andrade et al., 2000). The advantages of chemically induced DM animal models are that they are relatively simple and cheap (Dufrane et al., 2006) and the disadvantage is Streptozotocin and Alloxan can be toxic to other body organs (Lee et al., 2010). Another advantage is that both do mimic the pathological consequences of DM i.e. hyperglycaemia, glycosuria, ketoacidosis etc. Both can rapidly produce the symptoms of insulin deficiency. However, apart from toxicity a disadvantage is that they are T1DM models and this is not really a druggable condition and hence not ideal for investigating natural products that would treat T2DM.

3.2.4. Type 2 diabetes animal models

T2DM is characterised by insulin resistance and a diminished capacity for insulin secretion by β cells. Thus insulin resistance animal models are employed to investigate T2DM. Obesity is closely associated with T2DM progression linked through the fatty acid induced insulin resistance discussed above. Therefore obese

animal models are used in the investigations because they replicate human conditions. For example, obesity induced hyperglycemia models such as db/db mouse, KKAy mouse, and high fat fed animal models are employed to investigate T2DM. There are genetic models of obesity and T2DM e.g. ob/ob and db/db mice, fa/fa and OLETF rats. There are also non-obese genetic T2DM models e.g. Goto-Kakizaki (GK) rat. All require a mention and perhaps even an explanation e.g. role of hyperphagia and obesity. Then there are the obesity-induced models. There are many of these and most involve increased calorie intake through increased fat feeding or fructose feeding (the latter is very popular because it mimics human consumption of fizzy drinks) (King and Bowe, 2016; King, 2012).

3.3. Siddha / Tamil Medicine (சித்த / தமிழ் வைத்தியம் – Siththa / Thamil Vaiththiyam)

SM is based on Saiva philosophy (**சைவ சித்தாந்தம்** - Saiva Siththantham). Saivism or Saivam (**சைவம்** - Saivam) is one of the six branches of Hinduism religion (**இந்து சமயம்** – Inthu samayam) which reveres Sivaperuman (**சிவபெருமான்**) as the principle God. SM is believed to have originated in ancient Tamil regions in southern India in the era of BCE 10 000 to BCE 4 000 (NIS, 2015). It is currently practised mostly in Tamil speaking regions in India, SL, and around the world (AYUSH, 2010).

Siththa (**சித்த**) means "heavenly bliss" or "achieving perfection" or "established truth". A person who achieved this status and can relieve human suffering is called Siththar (**சித்தர்**). They are considered to be super humans with great intelligence, culture, and powers and spiritual scientists discovered and explained the association between human and nature by supernatural powers and experimental discoveries. There are 18 Siththars who have contributed to SM (NIS, 2015; ISM, 2011; Uthamaroyan, 1992; Piet, 1952): Agathiyar (**அகத்தியர்**), Thirumoolar (**திருமூலர்**), Bogar (**போகர்**), Konganar (**கொங்கணர்**), Therayar (**தேரையர்**), Korakkar (**கோரக்கர்**), Karuvooraar (**கருவூரார்**) , Idaikkaadar (**இடைக்காடர்**), Sattamuni (**சட்டைமுனி**), Suntharaananthar (**சுந்தரானந்தர்**), Iraamathevar (**இராமதேவர்**), Paampaatti (**பாம்பாட்டி**), Machchamuni (**மச்சமுனி**), Kuthampai (**குதம்பை**), Aluhannar (**அழுகண்ணர்**) , Ahappe (**அகப்பே**), Nanthithevar (**நந்திதேவர்**), and Kahapusundar (**காகபுசுந்தர்**). There are some general philosophical concepts of Siththars which include "food is medicine, medicine is food" (**உணவே மருந்து, மருந்தே உணவு** - unave marunthu, marunthe unavu) and "sound mind makes a sound body" (**மனமது செம்மையானால் மந்திரம் செபிக்க வேண்டா** - manamathu semmaiyaanaal manthiram sebikka vendaa) (NHPI, 2015). There are a few notable Sri Lankan Siddhars lived in north and east SL. Especially Yogarswami (**யோகர்சுவாமி**) who lived half a century ago and his guru Sellappa Swami (**செல்லப்பா சுவாமி**) are very well known around the world.

SM is less known to the western world because most of the Siddha literature are still in Tamil and have not been translated (Thas, 2008). However, it was recognised by Biomedicine as an alternative East Indian medicinal system predominant within Tamil communities (Stephen E.S., 2005). The aims of SM are to make the body perfect, imperishable, and promote longevity and it is the first medicinal system to emphasis health as the perfect state of mental, physical, moral, social, and spiritual element of humans (ISM, 2011).

As SM philosophy is developed in the medicinal, spiritual, and intellectual aspects, it provides equal importance to internal soul and external body, diagnosing methods especially urine investigation (நீர்க்குறி - neerkkuri), alchemy (converting base metals into gold) and materia medica (using enormous range of ingredients) are the uniqueness of SM over the other Traditional Medicines including Ayurveda (AYUSH, 2010; Narayansami, 1975). Currently SM is accepted as being suitable to treat all disorders expect emergency cases (AYUSH, 2010). Also herbomineral or herbometal preparations which contain nanoparticles are more effective in life threatening and chronic disorders (ISM, 2011).

The principle of SM is the 'universe-body' principle (அண்டபிண்ட தத்துவம் – andapinda thaththuvam) or the association between the universe and human body. The physical structure of the human body (உடல் தாதுக்கள் – udal thaathukkal) is composed of five elements (பஞ்சபூதங்கள் – panjapoothangal) which are earth (நிலம் – nilam), water (நீர் – neer), fire (நெருப்பு – neruppu), wind (வளி – vali), and sky (ஆகாயம் – aahaayam). Human body functions are retained by the physiological units (உயிர் தாதுக்கள் – uyir thaathukkal) also called three forces or faults, which are wind (வாதம் – vaatham), bile (பித்தம் – piththam), and phlegm (சிலேற்பனம் – siletpanam). Imbalance of these three forces causes illnesses (Narayansami 1975). Every living body is sustained by seven fundamental tissues (ஏழு தாதுக்கள் – elu thathukkal) which are, lymph (சரம் – saram), blood (குருதி – kuruthi), flesh (ஊன் – oon), fat (கொழுப்பு – koluppu), bone (எலும்பு – elumbu), marrow (மூளை – moolai), and semen (வெந்நீர் – veneer) (Shanmuka Velu, 1987). There are eight Siddha diagnostic methods: pulse examination (நாடி – naadi), touch (பரிசம் – parisam), tongue examination (நா – naa), body colour (நிறம் – niram), speech (மொழி – moli), eye (விழி – vili), stool (மலம் – malam), and urine (மூத்திரம் – moothiram). Another diagnotic method called urine investigation (நீர்க்குறி – neerkkuri) is a unique to SM. A sesame oil drop placed over urine and its shape and spreading patterns are observed. The fundamental principle of this diagnosis is linked to the surface tension of urine (Narayansami, 1975).

Sidhar Yugimuni (சித்தர் யுகிமுனி – Siththar Yuhimuni) identified 4448 disorders (ISM, 2011) and there are three types of treatments: divine (தேவ மருத்துவம் – theva maruththuvam), rational (மானிட மருத்துவம் – maanida maruththuvam),

and surgical treatment (அசுர மருத்துவம் – asura maruththuvam). Also there are three types of medications which are, miracle, sophisticated, and common medications. Drug ingrdeients are classified into three and they are herbal (தாவரம் வர்க்கம் – thaavaram varkkam), inorganic (தாது வர்க்கம் – thaathu varkkam), such as metals and minerals, and animal products (ஜீவ வர்க்கம் – jeeva varkkam) (NIS, 2015). More than 80 % are herbal products (ISM, 2011). Treatments are individual as they are provided considering environment, patient, age, sex, lifestyles, habitat, mental state, meteorological condition, appetite, physiological structure, and physical state which reduces diagnosis and treatment faults (AYUSH, 2010).

3.4. Antidiabetic Sri Lankan Siddha preparations sources

The documents used to obtain information on antidiabetic SL SM preparations are current university text books which were originally from SL and written in Tamil. They are used as teaching material in Bachelor of Siddha Medicine and Surgery (BSMS) degree in the universities in SL and thus form the basis for Siddha practice:

1. Pararasaseharam (Fifth Part) (பரராசசேகரம் (ஐந்தாம் பாகம்) - Pararaasaseharam (Ainthaam Paaham)): This book was compiled under King Pararaasaseharan (பரராசசேகரன்) between 1478 and 1519. It was initially printed as a book in 1935 by Ponniapillai, I. in Mallaaham and reprinted in 2003 by Sripathy Sarma, P. and published by Niyanthree Publication in Nallur, Jaffna, SL. (Anonymous, 2003).
2. Seharaasasehara Treatment (செகராசசேகர வைத்தியம் - Seharaasasehara Vaiththiyam): Contents of this book were compiled under King Seharaasaseharan (செகராசசேகரன்) between 1380 and 1414. It was first printed in 1927 by Ponniapillai, I. and reprinted in 2000 by the Provincial Department of Indigenous Medicine, Ministry of Health north and east Provinces. (Anonymous, 2000).
3. Siddha Medicinal Procedure (சித்த ஔடத செய்முறை - Siththa Audatha Seimurai): This book was compiled by S.M. Ponniah and I. Sabapathipillaiin 1980 and published by Department of Ayurveda, Ministry of Health & Indigenous Medicine. (Ponniah and Sabapathipillai, 1980).

Only Anonymous (2003) and Anonymous (2000) contain the information about the symptoms and causes of DM as well as information of preparations, however source three (Ponniah and Sabapathipillai (1980)) only contains information on preparations. SL origin preparations are only considered in this study and few preparations mentioned on source three were excluded as they were stated as Indian origin.

3.5. Characteristics of diabetes in Siddha Medicine

In the following causes and signs which are seen to the Siddha correspondence of DM are described. The description is based on Siddha texts and as such follows the principles of Siddha medical theory. Generic term Diabetes Mellitus (DM) is used, since a distinction of T1DM or T2DM is not meaningful in this context. In Pararaasaseharam (Fifth Part) (Anonymous 2003) DM is called as losing water

(நீரிழிவு – neerilivu; சலக்கழிச்சல் – salakkalichchal), water related disease (சலரோகம் – salaroham), and sweet urine (மதுமேகம் – mathumeham) in SM and it is characterised by frequently passing hot urine, passing foamy urine like a pearl (drop) of fresh honey in the water, and this is an incurable disease (Anonymous, 2003). It is grouped within the polyuria related conditions (மேகநோய் – mehanoi) of which there are 20 types. These are categorized into three groups: fire (பித்தமேகம் – piththameham) (6 types), wind (வாதமேகம் – vaathameham) (4 types), and water related polyuria conditions (சிலேற்பனமேகம் – siletpanameham) (10 types). Moreover, DM is considered as one of the wind related polyuria related condition.

3.5.1. Causes of diabetes

Consumption of ghee (semifluid butter), curd, and milk (which increase the coolness of the body), consumption of meat, not applying oil on the body, excessively walking in the sun, and excessive sexual intercourse with woman are considered to be causes of DM (நீரிழிவு – neerilivu) (Anonymous, 2000).

Consuming excess or dearth food (eating disorder), having meals at irregular times (irregular eating), excess consumption of ghee and milk, excessive consumption of sour foods and Irasam (இரசம்). Irasam is a decoction (common dish) which is served with meals especially lunch and it is prepared using *Cuminum cyminum* L. dried fruit (Apiaceae), *Coriandrum sativum* L. dried fruit, *Allium cepa* L. (Amaryllidaceae) fresh bulb, *A. sativum* L. dried bulb, *Tamarindus indica* L. (Fabaceae) dried fruit juice, *Piper nigrum* L. (Piperaceae) dried fruit, *Murraya koenigii* (L.) Spreng. (Rutaceae) fresh leaf, *Capsicum annuum* L. (Solanaceae) dried fruit, and *Curcuma longa* L. (Zingiberaceae) dried rhizome powder. Also having excessive sexual intercourse with a woman and excessively walking in the sun during summer may cause DM (Anonymous, 2000).

3.5.2. Signs of diabetes

The signs of DM (நீரிழிவு – neerilivu) include feeling laziness, excessive sweating, body odour, always wanting to sleep, dry tongue, grease formation on tongue, sweet taste in mouth, desiring to consume cold drinks and foods, dry chest and throat, rapid growth of hair and nail, and ants and flies gather around the urine (Anonymous, 2003).

The signs in Anonymous (2000) are somewhat different and include burning sensation in the stomach, paleness of body skin, weight loss, consciousness loss, dry tongue, feeling thirsty, excessive urination during the night (nocturia), difficulty in walking, blurred vision on humid, foggy, and rainy days, excessive urination, and feeling depressed.

Another set of signs is described including burning sensation in the stomach, sweating, difficulty in walking, blurred vision, wanting to quench thirst by drinking buttermilk (whey) and coconut water, loss of appetite, dry tongue, body ache, passing clear and foamless urine during day and night, extreme pain, ear congestion, and unable to fall asleep (insomnia) (Anonymous, 2000).

Additionally, sweet taste of urine, gathering of ants and flies on urine, passing urine with properties of coconut water during the night, dry tongue, feeling thirsty, body weakness, laziness are seen as signs and may cause death (Anonymous, 2000).

3.5.3. Types of diabetes

In SM 24 types of neerilivu (what according to the textbook is considered to be DM) are distinguished and further divided into seven categories. These categories are based on the impact the basic elements have on the human body and the types are identified based on the taste and odour of the urine. The seven categories are:

1. Wind associated DM (**வாத நீரிழிவு** – Vaatha neerilivu) including three types. The urine can be characterised by:
   - An odour of *Mangifera indica* L. (Anacardiaceae) flower and sour taste, or
   - An odour of *Crocus sativus* L. (Iridaceae) flower and sour-bitter taste.

2. Wind-fire associated DM (**வாதபித்த நீரிழிவு** – Vaathapiththa neerilivu) including four types. The urine can be characterised by:

   - An odour of *Curcuma longa* L. rhizome (Zingiberaceae) and sour-bitter taste,
   - An odour of *Nerium oleander* L. (Apocynaceae) flower and sweet-pungent-bitter-sour-astringent taste,
   - An odour of milk and buttery taste, and
   - An odour of brain odour and bitter taste.

3. Fire associated DM (**பித்த நீரிழிவு** – Piththa neerilivu) including three types. The urine can be characterised by:

   - An odour of fruit juice and bitter taste,
   - A salty odour and taste, and
   - An odour of *Jasminum sambac* (L.) Aiton (Oleaceae) flower and producing a burning sensation when urinating

4. Fire-wind associated DM (**பித்தவாத நீரிழிவு** – piththavaatha neerilivu) including two types. The urine can be characterised by:
   - An odour of cow urine and astringent taste and
   - An odour of *Santalum album* L. (Santalaceae) wood and peppery taste.

5. Water associated DM (**சிலேற்பன நீரிழிவு** – Siletpana neerilivu) including four types. The urine can be characterised by:
   - An odour of *Pandanus odorifer* (Forssk.) Kuntze (Pandanaceae) flower- cow manure-lemon-blood and sweet taste.

6. Water-fire associated DM (**சிலேற்பனபித்த நீரிழிவு** – Siletpanapiththa neerilivu) including four types. The urine can be characterised by:

   - An odour of *Magnolia champaca* (L.) Baill. ex Pierre (Magnoliaceae) flower,

- A taste like *Syzygium cumini* (L.) Skeels (Myrtaceae) fruit,
- A bad odour and a bitter-sour taste as well as ants gathering around the urine, and
- An odour of slaked lime (calcium hydroxide) and producing a burning sensation (similar to the one caused by lime (calcium oxide) when urinating.

7. Water-wind associated DM (சிலேற்பனவாத நீரிழிவு – Siletpanavaatha neerilivu) including four types. The urine can be characterised by:

- A strong odour and sour taste. (Sithamparthanuppillai, 1982).

3.5.4. Diabetes complications

Like in Biomedicine DM complications have been reported in SM. Some of the complications include lower abdominal pain, tiredness after urinating, flatulence , increased deficiency in sperm secretion, sperm in urine, general body weakness, loss of appetite, abscess formation, diarrhoea, unconsciousness, and death (Sithamparthanuppillai, 1982).

3.6. Methods

Information of the antidiabetic SL SM preparations were obtained from the text books which were written / complied and currently used in the universities in SL (see section 3.4. Antidiabetic Sri Lankan Siddha preparations sources). Scientific names of the plants used in the preparations are based on Sugathadasa et al. (2008) and validated on http://www.theplantlist.org. Since historical documents are used as a source in this work, there might be some discrepancies of the plant species mentioned in the original sources and botanically identified. Therefore all plant species names are validated taxonomically but the exact botanical identification is based on the information available in the historical and other archival documents only and based on the accepted names in these written sources. Both, accepted and synonym (in brackets), names are stated for those found on Checklist of Medicinal Plants of SL as synonym. The family names of the plant species were validated using APG III (2009).

In order to assess what is known in bioscientific and biomedical terms about these species, relevant literature was identified through Web of Science electronic database searches until January 2016. Antidiabetic pharmacology studies only associated with activities of reducing blood glucose levels and inhibition activity of enzymes such as α-amylase and α-glucosidase were considered and studies of DM complications were excluded. Also species stated in AHP (2011), Brendler et al. (2010), EMA (2009), Upton et al. (2011), WHOMSM1 (1999), WHOMSM2 (2004), WHOMSM3 (2007), and WHOMSM4 (2009) were excluded from further analysis and thus from the search. Both genus and species names together in double quotation marks (" ") was used as a primary search and the results were refined by using diabet* as a secondary search term.

4. Results and discussion

4.1. Siddha treatments for diabetes

DM is diagnosed by local Siddha healers and academic Siddha medical doctors by pulse reading and odour and taste of the urine and is not based on a biomedical diagnosis. Oral preparations such as pills, powders, decoctions, diets, oils as well as topical creams are used as preparations with pills are the most common formulation used. Preparations are provided at state Siddha hospitals which are manufactured in large scale by SL Ayurveda Drugs Corporation in SL and are also imported from India (MIM, 2013).

Preparations provided by local Siddha healers are prepared by themselves at their homes. Consequently, there is some variability in their composition if an ingredient is unavailable then it is simply left out. However, the absent ingredient(s) might be the principle component with more effect in that particular preparation. According to Siddha concepts, if such an 'incomplete' preparation is taken by the patients, the full recovery or effectiveness is not achieved affecting the reliability of Traditional Medicine treatments. On the other hand, preparations provided at state Siddha hospitals contain all the ingredients and as such seem to be more consistent in their composition.

Adjuvants like honey, decoctions or buttermilk are usually taken with these SM preparations, whereas, in Biomedicine no such adjuvants are used. Adjuvants are recommended; however, they are not supplied by either state Siddha hospitals or local Siddha healers. Therefore adjuvants have to be prepared by the patients. Diet management is currently recommended by Biomedicine and this is also recommended in SM. Dietary items are consumed together with the specific antidiabetic preparations. Again diets are not compulsory but are recommended for achieving better treatment outcomes. When consuming some preparations certain foods should be avoided. For example, fish, bitter and sour foods should be avoided while taking preparation 14 (Suravappidippaanundai - சுவறப்பிடிப்பாணுண்டை) (see Appendix B).

4.2. Comparison of diabetes concepts in Biomedicine and Siddha Medicine

Since Banting and Best's discovery in 1921 (Nobel Media AB, 2014) that an extract from cattle foetal pancreas lowers blood sugar levels of depancreatised dogs, DM has become a more and more prominent part of the biomedical research and practice. The typical biomedically recognised symptoms of DM are well known as is the treatment with associated changes in a patient's lifestyle (ADS, 2015).

There are some similarities and differences between Biomedicine and SM in definition, causes, types, diagnosis, treatment, and complications of DM. In SM (especially in the earlier textbooks) the causes of DM are linked to the consumption of unsuitable diets rich in animal fat and social behaviour (see section 3.5.1. Causes of diabetes) and not to biomedical changes in the human body. In both Biomedicine and SM DM is considered as a polyuria associated condition. Biomedicine defines DM as "excessive secretion of sweet urine" while SM defines as "passing foamy urine like a pearl of fresh honey in the water". Furthermore, both medicinal systems consider it as an incurable disorder and the symptoms such as frequent urination, excessive thirst, blurred vision and weight loss are also mentioned in both systems. In Biomedicine DM is classified into three types whereas in SM 24 types in seven

categories are distinguished. It is diagnosed by various blood tests in Biomedicine whereas SM uses a diagnosis based on the odour and taste of the urine. Biomedicine states that one the reasons for body odour or insomnia is DM, which are indicated as symptoms in SM. In Biomedicine Fuchs' dystrophy (build-up of fluids in cornea tissues in eyes) symptoms have been found to be more severe on a humid or rainy day and one of the diabetic ketoacidosis (a diabetic complication) symptoms, sweet taste in mouth, were mentioned as symptoms of DM in addition in SM (Anonymous, 2000). Moreover, in both systems, oral administration of medications is employed. In SM decoctions and powders may be used In SM uses topical preparations (e.g. oils and creams) may also be used while injections are used in Biomedicine. Biomedicine remedies are known to cause several unwanted adverse side effects while these are not mentioned in SM. Furthermore, as SM treatments are individual, it is assumed that they cause less or no side effects. However, there is no scientific evidence base for the latter.

4.4. Antidiabetic Sri Lankan Siddha preparations – an overview

4.4.1. Ethnobotanical analysis and types of plants used in the antidiabetic Sri Lankan Siddha preparations

Family and scientific name, Tamil name, part used, preparation, and source of 171 plants in 73 families which are recorded in the SL SM preparations used to treat DM are presented in Appendix A. The most frequently used species is *Senna auriculata* and the largest number of taxa is from the Fabaceae.

Detailed information of ingredient (scientific or English name), family (where applicable), amount used (converted to metric units from Tamil units where applicable), preparation procedure, and dosage of 60 antidiabetic SL SM preparations obtained from the sources earlier mentioned in the background and methods (see section 3.4. Antidiabetic Sri Lankan Siddha preparations sources) are not solely used to treat DM and they are also used to treat several other disorders which are not related to DM. There are several other common preparations also available to treat all 20 types of polyuria associated conditions. Preparations particularly mentioned to treat DM are only presented in this Appendix B. Anonymous (2003) contains the largest number of antidiabetic SL SM preparations followed by Anonymous (2000), and Ponniah and Sabapathipillai (1980). Oral and topical preparations are used to treat DM. Pills, powders, decoctions, diets, and oils/creams are used as oral medications and oils/creams are used as topical medications. pillas are the most common (nearly two thirds) preparation used, followed by powder, cream, decoction, diet, and oil. Pittu (பிட்டு) is a common diet which is prepared, usually with rice flour (sometimes with other grain flours such as *Vigna mungo* (L.) Hepper (Fabaceae), *Eleusine coracana* (L.) Gaertn. (Poaceae)), whereas preparations 4, 5, 6, and 7 (see Appendix B) are different types of pittu (பிட்டு) which are not commonly prepared. Preparations 44 (Santhanaathiyennai - சந்தனாதியெண்ணெய்), 46 (Piramehachchanthanaathiyennai - பிரமேகச்சந்தனாதியெண்ணெய்), and 47 (Neerilivuchchanthanaathiyennai -

நீரிழிவுச்சந்தனாதியெண்ணெய்) (see appendix B) are the only three topical preparations.

Plants, animal (including marine organism), and inorganic substances (minerals and metals) are used in the antidiabetic SL SM preparations. Almost all antidiabetic SL SM contain botanical drugs except preparation 41 (Piramehakkulihai - பிரமேகக்குளிகை) which contain only animal materials and preparation 42 (Piramehakkulihai - பிரமேகக்குளிகை) which contain animal and inorganic ingredients. More than two thirds of preparations contain only plant ingredients, the vast majority (97 %) contain botanical drugs. Combination of plant and inorganic materials, combination of plant, inorganic, and animal materials, and combination of plant and animal materials are far less common. Furthermore, the majority of the ingredients in the preparations containing combination of different types of ingredients are also botanical drugs. Preparations 16 (Salakkalichchalpalavukkum kaimarunthu - சலக்கழிச்சல்பலவுக்கும் கைமருந்து) and 53 (தூள் – Thool) contain only a single ingredient i.e. one botanical drug. This is highlighting the importance of the plants in antidiabetic SL SM preparations. Combinations of all three types of ingredients are only used in 13 preparations. Preparation 46 (Piramehachchanthanaathiyennai - பிரமேகச்சந்தனாதியெண்ணெய்), is the preparation which contains the most number (64) of ingredients including 54 plant species in 40 families. Almost all decoctions mentioned in Anonymous (2003) and Anonymous (2000) only contain plant materials with preparation 50 of Anonymous (2000) containing a combination of inorganic substance with plant material. Same plant part (bark) of different plant species are used in preparation 49 (Kudineer - குடிநீர்) whereas different parts of *Senna auriculata* are the only ingredients in preparation 24 (Salakkalichchalpalavukkum kaimarunthu - சலக்கழிச்சல்பலவுக்கும் கைமருந்து). Remarkably, almost all preparations containing only botanical drugs contain either toxic plant species or are from families known to yield many toxic species. Plant parts such as leaves, seeds, barks, stems, roots, fruits, flowers, rhizomes, and wood were used in antidiabetic SL SM preparations with seed being most commonly used.

4.4.2. Plants used against diabetes – the wider economical – botanical context

Many of the species are economically important, often cultivated / managed species and they are part of the wider Sri Lankan culture. Very often these species also have other uses such as a food, in ritual, in cosmetics and hygiene, as artefact, and as medicines used for other conditions.

A large number of well-known and widely used food plants including *Allium sativum*, *Curcuma longa*, *Tamarindus indica* , various *Piper* species like *P. cubeba*., *P. nigrum, Saccharum officinarum*, and *Zingiber officinale* are also part of DM preparations, as are diverse fruits *(Anacardium occidentale*, *Cocos nucifera, Phoenix dactylifera*, *Ph. pusilla., Punica granatum, Artocarpus heterophyllus*, *Musa × paradisiaca,* and *Syzygium cumini*). Various green leaves are consumed as a part of a daily diet in SL, the most commonly used are *Alternanthera sessilis*, *Ipomoea aquatica*, *Rivea ornata*, *Coccinia grandis*, *Mukia maderaspatana*, and *Murraya koenigii*. Spices can be defined as being any of various pungent, aromatic plant substances used to flavour foods or

beverages. *Cinnamomum verum, Myristica fragrans, Elettaria cardamomum,* and *Syzygium aromaticum* are the common spices used in and exported from SL. Grains are consumed as the main part of the diet and *Oryza sativa, Sesamum indicum, Vigna mungo, Cajanus cajan, Eleusine coracana, Panicum sumatrense, Paspalum scrobiculatum* are the most commonly used.

As SM is based on Saiva philosophy (**சைவ சித்தாந்தம்** - Saiva Siththantham) several plants used in Saiva rituals such as *Elaeocarpus tuberculatus, Myroxylon balsamum, Cinnamomum cappara-coronde, Aegle marmelos, Azadirachta indica, Santalum album*, and *Curcuma aromatica* are part of ingredients in the preparations. *Crocus sativus, Chrysopogon zizanioides, Santalum album,* and *Curcuma aromatica* the natural cosmetic substances used in Tamil tradition for centuries. In Saiva and Tamil traditions *Ficus benghalensis* aerial root and *Azadirachta indica* tender stem have been used to brush teeth also for centuries.

Furniture is mostly made by heartwood which is strong and long lasting, such as *Acacia chundra* and *Azadirachta indica* are commonly used in SL. Moreover, plant used to obtain cotton wool and manufacturing cloth (*Gossypium arboretum*) and handicrafts (*Bambusa bambos, Cocos nucifera,* and *Borassus flabellifer*), aquatic plants (*Nelumbo nucifera* and *Nymphaea pubescens*), coastal plant (*Pandanus odorifer*), incense plants (*Myroxylon balsamum* and *Santalum album*) are also included in the preparations. Some plants such as *Musa × paradisiaca, Cocos nucifera,* and *B. flabellifer* are used for several purposes in daily life whereas each part of these plants has several uses.

Many are locally used common medicinal plants with a wide distribution throughout south Asia and other continents such as *Justicia adhatoda*, *Acorus calamus*, *Terminalia chebula*, *Ricinus communis*, *Vitex negundo*, *Azadirachta indica*, *Coscinium fenestratum*, and *Aloe vera*. Weeds, i.e. species which are successful in disturbed environments, fast growing, and, often but not always herbaceous (Zimdahl, 1992) are, as in other medical traditions, employed frequently. Some of the weeds used include *Cyperus rotundus*, *Euphorbia hirta*, *Boerhavia diffusa*, *Phyllanthus amarus* or *Tribulus terrestris*. Apart from the medicinal benefits, some weeds are also used as foods. For example, *Achyranthes aspera* and *Cardiospermum halicacabum*.

4.5. Animal parts used

More than one third of preparations contain animal parts as ingredients. Male deer musk (produced in a glandular sac in the lower abdomen), deer horn, civet musk (secreted in anal scent glands), rhinoceros horn, cow gallstone and urine, human colostrum (foremilk), ant egg, *Coccus lacca* (Shellac – resin excreted by the females of the lac insect) are used, cow gallstones are the most frequently used. Deer horn is used in calx form. Civet musk and rhinoceros horn are rare and they will be unavailable in the future. Also it is illegal to possess trade or use them. In addition, marine organisms such as pearl and red coral are also used in some preparations.

4.6. Inorganic substances used

Nearly half of the preparations contain inorganic ingredients. Metals such as mercury, arsenic, iron, silver, gold, zinc, and lead as well as minerals such as rock salt, borax, cinnabar, biotite (black mica), saltpetre (potassium nitrate), Roche alum, graphite, beryl, asbestos, gypsum, stibnite (contains antimony sulphide), mica

(aluminium silicate), and magnetite, and sulfur are used in antidiabetic SL SM preparations. Magnetite is the most frequently used substance. Many of these substances are often highly poisonous (mercury, arsenic, etc.). Silver and gold are used in calx form whereas borax, cinnabar, and graphite are used in purified form. There are some studies which evaluated the toxicity of some inorganic substances used in Traditional Medicines. Biotite, for example, is used in several antidiabetic SL SM preparations. Biotite ash with different drug vehicles did not show any systemic toxicity (Srinivasa et al., 2010) and no genotoxicity in *in vivo* micronucleus assay and comet assay in Wistar rat of both sexes (Vardhini et al., 2010). 'Detoxification procedures' are employed in the preparation procedures while using some of these substances. For example mica (Wijenayake et al., 2014). Clearly such practices are of major concern and toxicological risks need to be addressed.

4.7. Amount of ingredients and dosages used

The amount of ingredients and dosages were converted from Tamil units where applicable and are presented in metric units (Appendix B). Standard Tamil weight measures, such as palam (பலம், 1 பலம் = 40 g), panaavidai / kaasidai (பணாவிடை / காசிடை, 1 பணாவிடை = 488 g), and kalanju (கழஞ்சு, 1 கழஞ்சு = 5 g) are used, whereas marakkaal (மரக்கால், 1 மரக்கால் = 1200 ml), naali (நாழி, 1 நாழி = 600 ml), kalam (கலம், 1 கலம் = 57.6 l) and koththu (கொத்து, 1 கொத்து = 150 ml) are used to measure volume of liquids. Moreover, nonstandard Tamil units such as 1 handful (1 பிடி – 1 pidi) – including half handful (½ பிடி – ½ pidi) and one quarter handful (¼ பிடி – ¼ pidi), size of a small coconut (சிறு தேங்காயளவு – siru thengaaiyalavu), as required (தேவையானளவு – thevaiyaanavalavu), size of an *Areca catechu* L. (Arecaceae) seed (பாக்களவு – paakkalavu = 5 g), and lemon size (எலுமிச்சங்காயளவு – elumichchangkaayalavu) are also used.

Tamil units such as size of an *Areca catechu* seed (5 g) have been standardised to equivalent in metric units. However, other Tamil units like one handful or half handful have not been standardised into metric units. Using non-standardised metric units would lead to inconsistency in the preparations because measured amount of ingredients would vary from one region to the next (lemon size, size of a small coconut etc.), and from person to person (handful, half handful, and one quarter handful). Therefore, it is recommended to standardise these units into metric units and encourage Siddha preparation manufacturers including local Siddha healers to use exact amounts during manufacturing and prescription.

Most of the formally described preparations (see Appendix B) and preparations produced by local Siddha healers (passed on orally through the generations) are still used in SL today. However, local Siddha healers do not reveal any information about the preparations prescribed by them and it is only passed to the next generation as a secret.

5. Pharmacological information on individual species

While in the previous parts at the composition and use of SL SM preparations were assessed, this part aims to assess the individual species in terms of the ethnopharmacological properties that made them suitable for use as antidiabetic remedies. Focus was exclusively on individual species used in SM since:

1. The evaluation does not cover the complex preparations as such since no or insufficient information on these preparations is available and since at this stage it is not scientifically feasible to evaluate such multicomponent mixtures.

2. None of the 60 antidiabetic SL SM preparations (Appendix B) have been studied scientifically. Therefore, the pharmacological studies relevant for anti-diabetic activity of individual species used in those 60 preparations were reviewed.

Systematically reviewed information on the pharmacology studies such as parts used, pre-treatment of plant parts, extraction method, (active) compounds / fractions / extracts, model, dosage / concentration, duration, way of administration, maximum nontoxic dosage and duration, and reference are presented in Appendix C. Pharmacological information relevant for understanding secondary complications of DM is not included.

5.1. Pretreatment of plant part and extraction

SM uses a range of methods for drying the botanical drugs including the use as fresh material (incl. pressed juices), shade or sun dried. However, in the pharmacological experiments mostly shade dried biomasses were employed. In some cases fresh materials were used. Solvents such as methanol, water, ethanol, mixture of different percentage aqueous ethanol were used in extraction procedures however, ethanol is most frequently used. In SM water and plant part juices are usually used as solvents. Thus future research should pay closer attention to such SL SM preparation practices especially the use of fresh plant material. Only when fresh material is unavailable solvent extraction of dried material should be employed whereas fresh plant material available freeze dried plant part juices should be employed as extracts for screening and further studies. Moreover, investigating the plant part used in Traditional Medicine would provide more positive results in pharmacology studies rather than trying a different one.

5.2. Levels of evidence

About 28 % (48 out of 171) of the overall species recorded (Appendix A) are globally distributed and used. These are very well studied such as *Allium sativum*, *Zingiber officinale* which were excluded from the further analysis and the scientific literature of the total 123 species were reviewed. The species studied for anti-diabetic activity (Appendix C) can be categorised into four levels based on the models used and other evidence available:

- Species which have not been studied at all for antidiabetic related activities or did not show anti-diabetic activity ,

- Limited *in vitro* evidence and active compound identified,
- *In vivo* evidence and active compound identified, and
- Clinical evidence and active compound identified available.

5.2.1. Species which have not been studied at all for antidiabetic related activities or did not show antidiabetic activity

Nearly 41 % (51 out of 123) species reviewed have either not been studied at all or did not show anti-diabetic activity including *Lannea coromandelica*, *Piper cubeba*, *Trachyspermum roxburghianum, Phoenix pusilla,* and *Saccharum officinarum*. Species such as *Limonia acidissima, Nymphaea pubescens, Hyoscyamus reticulatus, Aconitum heterophyllum, Cinnamomum cappara-coronde, Cissampelos pareira, Mesua ferrea*, and *Acacia chundra* are used individually in five or more preparations thus it is recommended to study the anti-diabetic activity of these species in either *in vitro* or *in vivo* models.

5.2.2. Limited *in vitro* evidence and active compound identified

According to the studies listed in Appendix C, α- and β-glucosidase, as well as α-amylase inhibition, glycogen synthesis assays, and 3T3-L1 cell line were employed to investigate anti-diabetic activity in *in vitro* studies. The α-glucosidase inhibition assay was most frequently used. As mentioned above, approximately 90 % of people have DM globally have T2DM (WHO, 1999). Therefore, bioassays which are closely related to T2DM mentioned in section 3.2.1. *In vitro* models should be employed in future studies.

Only 6 % (7 out of 123) of species reviewed such as *Anacyclus pyrethrum*, *Bambusa bambos*, and *Gossypium arboretum* had been studied only in *in vitro* bioassays and AAwas observed. *Abrus precatorius* is the most frequently studied within the species studied up to this level. Higher and lower concentrations of extracts were employed in some of the species studied up to this level. Ethanol extract (29.25 µg/ml) of *A. pyrethrum* dried root showed inhibitory effect in the α-amylase inhibition assay (Kumar V.K. and Lalitha, 2014). Also an aqueous extract (10.10 mg/ml) of *G. arboreum* dried leaves exhibited potent inhibitory activity in α-amylase inhibition assay (Kazeem et al., 2013).

Active compounds have been identified only from *A. precatorius* and *Dichrostachys cinerea.* Three compounds (Lupenone, 24- methylenecycloartenone, and Luteolin) were identified from *A. precatorius* dried leaf, 50 % methanol extract detected a potent inhibitory activity in α-amylase inhibition assay (Yonemoto et al., 2014). The active compounds of the rest of the species should be identified and both these species and their antidiabetic active compounds should be studied in further *in vivo* models. However, this is the lowest level study of pharmacology evidence and provides insufficient evidence.

5.2.3. *In vivo* evidence and active compound identified

T1DM and T2DM animal models (see 3.2.12. *In vivo* models) were employed to study anti-diabetic activity (Appendix C) using animal models such as rat, mouse, and rabbit with rat being the most frequently used animal. The majority of the studies were done in T1DM models (esp. Streptozotocin - induced diabetes) rather than T2DM models. T2DM models are db/db, KKAy, and high fat fed animal models with the db/db animal model being the most frequently employed one.

Nearly 48 % (59 out of 123) of species reviewed including *Tamarindus indica*, *Thespesia populnea, Ficus religiosa, Phyllanthus amarus,* and *Alpinia galangal* have been studied up to this level. *Syzygium cumini* is most frequently studied in *in vivo* models within the species studied up to this level. As mentioned before higher and lower dosages of extracts were employed in *in vivo* studies. In some studies using T1DM models lower dosage such as 5 mg/kg showedanti-diabetic activity . For an example 70 % methanol extract (5 mg/kg) of *Musa × paradisiaca* shade dried sucker orally administrated to Alloxan induced diabetic rat for 21 d decreased elevated blood glucose level (Akinlolu et al., 2015). In T2DM models ethyl acetate fraction of ethanol extract (100 mg/kg) of *Acorus calamus* dried radix orally administrated for 3 weeks to db/db mouse significantly reduced serum glucose (Wu H. et al., 2009). High dosage such as 4000 mg/kg was also employed in some studies. For an example aqueous extract (4000 mg/kg) of *Alpinia galangal* dried rhizome orally administrated to Alloxan induced diabetic rabbit for 6 h significantly lowered the blood glucose level (Akhtar M.S. et al., 2002). However, this study did not reveal any toxicity of this dosage and the extremely high dose casts serious doubts at the pharmacological relevance of such data.

Antidiabetic active compounds have been identified in 12 species including *Acorus calamus, Areca catechu, Cheilocostus speciosus, Myristica fragrans,* and *Plumbago zeylanica.* The majority of active compounds (five) have been identified in *Oroxylum indicum.* In T1DM models, β-amyrin palmitate (50 µg/kg) from *Hemidesmus indicus* root orally administered to Alloxan induced diabetic rat for 15 d showed remarkable lowered blood glucose levels (Nair et al., 2014). Whereas in T2DM models, macelingan (10 mg/kg) from *Myristica fragrans* seed kernel orally administrated to db/db mouse for 14 d also reduced serum glucose (Han et al., 2008).

Toxicity of active extracts and compounds were investigated in many studies. For example both aqueous and methanol (4000 mg/kg) extracts of *Achyranthes aspera* shade dried whole plant were orally administered to Alloxan induced diabetic rabbit decreased blood glucose levels in 4 h. However, toxicity study of this extract up to 8000 mg/kg for 7 d revealed as nontoxic (Akhtar M. and Iqbal, 1991). As the highest dosage is nontoxic and half of the nontoxic dosage showed antidiabetic effects in shorter time this plant possesses promising antidiabetic properties. Mycaminose (2000 mg/kg) identified from *Syzygium cumini* air dried mature seed administered to Streptozotocin induced diabetic rat for 14 d was revealed as nontoxic (Kumar A. et al., 2008). As higher dosage of this active compound showed not to be toxic this compound possesses a strong anti-diabetic activity, but again the relevance of is very doubtful due to the administered dosage. Hence, the antidiabetic active compound of the rest of the species showing anti-diabetic activity in *in vivo* models should be identified and both the species and their active compounds should be further studied in clinical models. Additionally, T1DM animal models are more frequently employed compared toT2DM models. As majority of the people have T2DM, more T2DM related animal models mentioned in section 3.2.4. Type 2

diabetes animal models should be therefore employed in *in vivo* antidiabetic pharmacological studies in the future.

5.2.4. Clinical evidence and active compound identified

T1DM, T2DM, and healthy volunteers were employed to investigate the anti-diabetic activity at this level with T2DM studies being the most frequently employed ones (Appendix C). Again as the aim is to study the anti-diabetic activity diabetic subjects should be employed. Employing normal subjects would lead to results of limited relevance.

Approximately 5 % (6 out of 123) of the species reviewed have clinical evidence including *Cyanthillium cinereum*, *Salacia reticulata,* and *Ficus racemose*. An aqueous extract (1200 mg/d) of *Ficus racemosa* bark orally administrated to T2DM patients (18 men and 12 women who has T2DM for less than a year) for 1 month as the only treatment showed a significant reduction in fasting blood glucose concentration (Ahmed et al., 2011). This is the lowest dosage of an extract studied that showed efficacy in the group of plants studied up to this level. Hot water extract (equivalent to 20 g/kg of starting material) of *Artocarpus heterophyllus* mature leaf was administered orally to 20 normal and diabetic volunteers in each group 1 h before glucose loading. Reduced blood glucose level was observed after 30 min of glucose administration (Fernando et al., 1991). DM is a chronic disorder thus a chronic clinical study would provide more accurate results. A preparation (6 g/d) containing *C. cinereum* root (as well as unspecified ingredients) was administrated for 6 months orally to T2DM sufferers (who had the disease for more than 6 months) significantly decreased blood glucose levels (Bin Sayeed et al., 2013). This is a very high dosage. However, it is not reported how much *C. cinereum* root was present in the preparation.

Antidiabetic active compounds (β-sitosterol, stigmasterol, and lanosterol) were only identified in *Ficus racemosa* within the plant species studied up to this level. Thus, it is recommended to identify the active compounds of the other species and in a next step these compounds should be studied in *in vitro, in vivo,* as well as clinical levels.

5.3. Toxic plants

Toxicity investigations play a very important role in assessing the therapeutic benefits of drugs and medicines derived from them. From the bibliographic data such as Roth et al. (2012) and Harborne et al (1996) some species may well have acute or chronic toxicity as well as posing the risk of teratogenicity and carcinogenesis as well as of allergic reactions. Nearly 49 % (60 out of 123) of plant species and various parts used in antidiabetic SL SM preparations were catagorised as toxic including *Abrus precatorius*, *Strychnos potatorum*, *Aconitum heterophyllum*, *Hyoscyamus reticulatus*, and *Cycas circinalis.* However, a toxicity assessment of the plants used in antidiabetic SL SM preparations is beyond the scope of this manuscript.

6. Conclusion

This is the first study systematically assessing the importance of preparations and plants used in antidiabetic SL SM preparations. It documents the importance of such

treatments and creates the basis for a more methodical study of these local resources. This review documents 60 preparations and 171 species (in 73 families) used to treat DM in SL SM. Botanical drugs are very important in antidiabetic SL SM preparations and the most frequently used species is *Senna auriculata*. Currently, non-standardised units for ingredient measurements in the preparations and dosages are used; these need to be converted into standardised units.

None of the 60 preparations documented in this review have been studied scientifically at all in any previous models. However, considerable pharmacology information on extracts of individual species is available. Therefore, anti-diabetic activity and toxicity of all preparations presented in this work should be scientifically studied using *in vitro*, *in vivo*, and clinical models in order to better understand their safety, pharmacological effects and clinical efficacy. Simple, preparations containing inexpensive, nontoxic, and common plant materials (such as preparations 25, 26, 27, 28, 29, 49, 50, and 51) ingredients used preparations are the most suitable candidates for further scientific investigations such as a full characterisation of their chemical composition. Plant extracts contain mixtures of active, partly active, and inactive compound. The bioactivity of a plant extract is not dependent on a single compound thus, due to this complexity, results from bioactivity assessments are often not reproducible (Heinrich, 2010). Therefore, a clear phytochemical characterisation, using for example metabolomics techniques linked with *in vitro* or *in vivo* screening for bioactivity and toxicity, can be used for a better characterisation of phytomedicines.

Indigenous and local medical knowledge has advanced and also made a greater contribution to global healthcare. Improvement of this knowledge base required that it incorporates evidence-based approaches to its practice. SM preparations produced by Sri Lanka Ayurvedic Drug Corporation (under the Sri Lankan Ministry of Indigenous Medicine) are believed to be consistent. On the other hand, SM preparations produced by Siddha healers have no assessment to be proved that they are consistent. Therefore, Sri Lankan Ministry of Indigenous Medicine should introduce new stricter laws to register the preparations, preparation methods, and ingredients, storage conditions, and shelf life prepared by local Siddha healers in terms to follow the consistency of SM preparations. Additionally, Sri Lankan Ministry of Indigenous Medicine should also carry out regular inspections to confirm the reliability of the preparations prepared by Siddha healers. Keeping information on such preparations secret or only accessible in a limited way would ultimately lead to its disappearance in the near future. Also any healers who are not willing to reveal the essential information on such preparations they use should be barred from registering and practising. Improved regulations of SM will also the likelihood of exclusion and avoidance of toxic materials such as mercury and arsenic being used in preparations.

Yet, as there is no SL SM pharmacopoeia available. Hence, it is recommended to develop and published such a legally binding document in the near future which would be used as an important teaching material in SM education, regulations ,and easier for the Siddha healers and Siddha academic doctors for identifying and treating disorders.

SM has been used for hundreds of years and it has shown numerous benefits, such as affordability, and ease of access, etc. Apart of these advantages, it also has certain limitations and one of the main ones being certain ingredients such as rhinoceros horn and rare plant species are difficult to come by and in some cases illegal to

handle. Therefore rare plant species which considered as important in the preparations should be cultivated to prevent from disappearance in the near future. Most of the pharmacology studies have been carried out in T1DM models. However, as stated above approximately 90 % of diabetics suffer from T2DM. Therefore, it is necessary to carry out further investigations in T2DM models. Fresh juices of various parts of plants are used as solvent in several antidiabetic SL SM preparations, for example, preparation 1. Hence, freeze dried fresh juices of plant materials could be used to study the pharmacological investigations where available, easily obtainable, and appropriate. Also, the pharmacological studies reviewed are often methodologically problematic for other reasons, including, for example, unrealistic high doses or poor general design. Therefore, in the future more rigorous experimental approach will be needed. Additionally, the pharmacology studies of preparations containing only organic substances (expect some minerals and metals), should be tested and where they give better outcomes then, those organic substances can be excluded from future preparations. Further studies also should be performed to identify potential drug – drug interactions and side effects caused. One of the objectives of this work is to make such information publicly available to prevent its disappearance in the future and to ascertain that the local and traditional knowledge is promoted internationally. Only if this information is in the public domain will it be possible to establish that this knowledge is based on SM. Lastly, this work builds the foundation for a more efficient study of antidiabetic SL SM preparations and the plants used.

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Graphical abstract

Ethnobotanical analysis

Review of antidiabetic preparations in classical and modern university textbooks of Sri Lankan Siddha Medicine

171 plant species in **73** families

48 globally distributed and used species

Ethnopharmacological analysis

123 species reviewed

- **41 %** either not studied at all or did not show antidiabetic activity
- **6 %** *in vitro* evidence
- **48 %** *in vivo* evidence
- **5 %** clinical evidence