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REVIEW ARTICLE

Medicinal Plants in Management of Diabetes Mellitus: An Overview

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Abstract: Diabetes mellitus has become a global epidemic over the past few decades and is one among the major causes of death worldwide. Although various modern medicines are in the market, herbal medicines have usually maintained worldwide popularity in achieving the primary health care needs of the diabetic population because of the multiple adverse effects related to them. Herbal medicines have a prolonged history of being used as medications and sources of medication for diabetes mellitus. Some of them are enclosed within the modern therapeutic arsenal of medicine, and others are used as complementary therapy or as dietary supplements by patients with diabetes. The present review describes on traditional antidiabetic herbal medicines with an emphasis on scientific investigations conducted on antidiabetic medicinal plants, polypherbal mixtures, isolated compounds and their associated toxicities.

Keywords: Antidiabetic compounds, antidiabetic medicinal plants, diabetes mellitus, polypherbal mixtures, toxicity of antidiabetic agents.

INTRODUCTION

Diabetes mellitus has become a devastating health problems nowadays and millions of people are fighting with this dilemma worldwide. Diabetes mellitus is an endocrine disease characterized by hyperglycaemia which occurs as a result of the inability of the pancreas to secrete insulin, defects in insulin action or both (ADA, 2013). Hyperglycaemia results in both microvascular and macrovascular complications which lead to long-term failure of various organs (Chawla *et al.,* 2016). Although numerous synthetic antidiabetic drugs are available, these medications have limitations in their use due to unwanted side effects (Chaudhury *et al.,* 2017). Hence, herbal products have been accepting a great demand for the management of diabetes due to low cost, high availability and less side effects.

The dependence of human beings on medicinal plants dates back to the beginning of life. Medicinal plants include various types of plants used for numerous medicinal purposes (Jamshidi-Kia *et al.,* 2018). During the past two decades, medicinal plants have become a topic of global importance. World health organization (WHO) estimated that 80% of world population relies on medicinal plants (Gopl *et al.,* 2014). In spite of the presence of effective modern allopathic medicines, herbal medicines have often maintained global popularity in meeting the primary health care needs. Concurrently, many people in developed countries have begun to turn to alternative or complementary therapies with medicinal plants. However, there is a paucity of scientific research data on medicinal plants.

According to WHO reports, around 21,000 plant species have the potential for being used as medicinal plants (Modak *et al.,* 2007). There have been significant developments in the pharmacological evaluation of various medicinal plants used in traditional systems of medicine in the treatment of many of the chronic diseases. Diabetes mellitus is one of them. Importantly, the treatments using medicinal plants are considered safe with little or no side effects independent of the age or gender of the patients. Furthermore, medicinal plants are considered as rich resources of phamacophores which can be used in drug development. In addition, medicinal plants play critical roles as important sources of nutrition.

The present review is an overview of diabetes mellitus, traditional medicines used in the management of diabetes mellitus, summary of antidiabetic medicinal plants, medicinal plants grown in Sri Lanka with scientifically proven antidiabetic activity, polyherbal mixtures with proven antidiabetic activity and toxicities of antidiabetic medicinal plants and polyherbal mixtures.

Diabetes mellitus has become a global epidemic and is considered as one of the emerging global health problems. The prevalence of diabetes has rapidly increased over the past few decades (WHO, 2016). Patients with diabetes have a high risk of morbidity and mortality than the healthy population. Globally, according to the International Diabetic Federation (IDF) Atlas, there were 425 million people with diabetes worldwide in 2016 (Ogurtsova *et al.,* 2017).

Many efforts have been devoted to search and develop optimal therapeutic agents for the management of diabetes mellitus. Due to various side effects associated with currently available oral antidiabetic drugs and their high cost, most of the diabetic patients especially in developing countries tend to use herbal plant remedies as alternative therapies for the management of diabetic mellitus (Ekor, 2014).

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Traditional herbal medicines for the management of diabetes mellitus

The use of traditional medicine continues to play a crucial role in the healthcare delivery systems of many parts of the world. Indeed, according to WHO, 40 % of the total population relies on traditional medical systems directly or indirectly (Mazid *et al.,* 2012), while 80% of the population in developing countries depend almost exclusively on traditional medical practices, more specifically, plant medicines for their primary health care needs (Karunamoorthi *et al.,* 2013). Reports from developed countries also indicate that several diabetic patients are gradually turning to herbal remedies as alternatives to modern synthetic drugs (Rani *et al.,* 2015). The literature on medicinal plants with hypoglycaemic activity is vast. More than 1200 species of plants have been used ethno-pharmacologically to treat for diabetes mellitus (Delaviz *et al*., 2017). Traditional systems of medicines always have played a significant role as therapeutic aid for the management of diabetes mellitus. In South East Asia, there is a vast volume of literature on traditional medicine. Generally, civilization has adopted broad cultural aspects which led to create different types of traditional medicine systems for over 3000 years. There are four main systems of traditional medicine in Sri Lanka namely; Ayurveda, Siddha, Unani and Deshiya Chikitsa (Waisundara and Watawana, 2014). The Ayurveda and Deshiya Chikitsa systems use mainly plants and herbal preparations for the treatment of diabetes mellitus as single plants or plant mixtures. Sri Lankan traditional physicians regularly use many antidiabetic plants such as *Momordica charantia* (Bitter melon), *Allium sativum* (garlic), *Annona squamosa* (sugar apple), *Gymnema sylvestre* (Gymnea), *Syzygium cumini* (Malabar Plum), *Allium cepa* (onion) *etc.* for their daily prescriptions.

Natural products derived from medicinal plants play an important role as useful tools in pharmacological studies in the management of diabetes mellitus (Farzaei *et al.,* 2015). Researchers have proved that the antidiabetic activity of medicinal plants is due to the presence of phenolic compounds, flavonoids, terpenoids, coumarins and other ingredients which demonstrate hypoglycaemic activity (Aswathy and Jessykutty, 2017). In many cases, the detailed mechanisms of action of traditionally used antidiabetic plants are unknown or inconclusive (Patel *et al.,* 2012). As such, many studies are being conducted to elucidate the mechanisms of action of different plants and natural compounds (Grover *et al.,* 2002). Medicinal plant extracts are mainly responsible for regenerating the function of pancreatic tissues by elevating the insulin output or inhibiting the intestinal absorption of glucose or by facilitating metabolites in insulin dependent processes (Patel *et al.,* 2012). Some widely used antidiabetic medicinal plants that were recently scrutinized by scientific investigations are summarized in Table 1.

Table 1: A summary of antidiabetic plants which were recently scrutinized by scientific investigations.

Family	Plant	plant part	Extract	Type of Study	Reference
Alangiaceae	*Alangium lamarckii*	Leaf	Methanol	Streptozotocin nicotinamide induced rats	Kumar *et al.,* 2011
Alliaceae	*Allium sativum*	Bulb	Ethanol	Normal and streptozotocin-induced rats	Eidi *et al.,* 2006
	Annona squamosa	Leaf	Aqueous	Streptozotocin-nicotinamide induced rats	Shirwaikar *et al.,* 2004
Apocynaceae	*Catharanthus roseus*	Leaf	Aqueous	Streptozotocin-induced diabetic rats	Rasineni *et al.,* 2010
	Tabernanthe iboga	Root, bark	Aqueous	Rat pancreatic islets	Souza *et al.,* 2011
Caesalpiniaceae	*Bauhinia variegata*	Stem bark	Aqueous	Alloxan induced hyperglycaemic rats	Kumar *et al.,* 2012
Cornaceae	*Cornus officinalis*	Fruit	Aqueous	Streotozotocin Induced diabetic rats	Han *et al.,* 2014
Cucurbitaceae	*Coccinia grandis*	Leaf	Aqueous	Streptozotocin-diabetic rats	Attanayake *et al.,* 2016
Fabaceae	*Medicago sativa*	Seed	Aqueous	Alloxan induced diabetic rats.	Helal *et al.,* 2013
Gentianaceae	*Enicostemma littorale*	Plant	Aqueous	Alloxan induced diabetic rats	Maroo *et al.,* 2003
Ginkgoaceae	*Ginkgo biloba*	Plant	Aqueous	Streptozotocin-induced diabetic rats	Cheng & Li 2012
Liliaceae	*Aloe vera*	Plant	Aqueous	Streptozotocin induced diabetic rats	Bahmani *et al.,* 2014
	Asparagus racemosus	Root	Ethanol	Streptozotocin-induced diabetic rats	Hannan *et al.,* 2012
Leguminosae	*Bougainvillea spectabilis*	Bark	Ethanol	Alloxan- induced diabetic rats	Jawla *et al.,* 2012
Rutaceae	*Aegle marmelos*	Seed	Aqueous	Diabetic rat	Kesari *et al.,* 2006
	Syzygium cumini	Seed	Ethyl acetate	Streptozotocin- induced diabetic rats	Kumar *et al.,* 2013

Sri Lankan medicinal plants with antidiabetic activity

The majority of rural population in Sri Lanka use indigenous medicinal systems for their primary health care. Considerable numbers of patients with diabetes mellitus have frequently used herbal supplements in the management of diabetes mellitus (Ediriweera and Ratnasooriya, 2009). However, only a few scientific studies have been reported on detailed antidiabetic mechanisms of medicinal plants in Sri Lanka. The studies on *P. embelica*, *P. marsupium*, *C. auriculata* confirmed the antihyperglycaemic effects of the selected plant extracts via the retardation of carbohydrate metabolizing enzymes (Abesundara *et al.,* 2004). The decoctions of Sri Lankan medicinal plants as *Salacia reticulata* (Celastraceae) *Aegle marmelos* (Rutaceae) and *Momordica charantia* (Cucurbitaceae) have shown potent hypoglycaemic activity in laboratory animals (Karunanayake *et al*. 1984). Fernando *et al* (1991) studied the hypoglycaemic activity of some Sri Lankan plants including *Artocarpus heterophyllus*, *Bambusa oulgaris and Osbeckia octandra*. The above plant extracts exerted potent antidiabetic activity *in vivo*. The stem bark of *Gmelina arborea*, *Kokoona zeylanica*, *Spondias pinnata*, *Syzygium caryophyllatum*, arial parts of *Scoparia dulcis*, *Sida alnifolia*, and roots of *Languas galanga* and leaves of *Coccinia grandis* were also evaluated on antihyperglycaemic activity by Attanayake *et al.,* (2013a, 2016b). Furthermore, Arambewela *et al.,* (2005) scrutinized the antidiabetic activities of the aqueous and ethanolic extracts of *Piper betle* leaves in Wistar rats. A report by Arambewela *et al.,* (2004) revealed the hypoglycaemic and antihyperglycaemic activities of the aqueous and the ethanolic extracts of *Alpinia calcarata* rhizomes in rats. Moreover, Sudasinghe *et al.,* (2018) reported on hypoglycaemic and hypolipidaemic activities of the aqueous leaf extract of *Passiflora suberosa*. In addition to the work on the above Sri Lankan higher medicinal plants, antidiabetic compounds namely, zeorin, methyl β-orcinolcarboxylate and methylorsellinate have been isolated from the Sri Lankan lichen *Cladonia* species (Karunaratne *et al.,* 2014; Thadhani and Karunaratne, 2017)

Antidiabetic compounds reported from medicinal plants

Bioactive compounds isolated from medicinal plants are in much demand than the synthetic compounds as antidiabetic drug leads owing to rich availability, efficacy and less side effects. Among the drugs approved in the therapy of diabetes in the last ten years, 49% are derived from plants (Gothai *et al.,* 2016). More than 1200 antidiabetic compounds from medicinal plants have been discovered by scientists all over the world (Trojan-Rodrigues *et al.,* 2012). The antidiabetic activities of isolated compounds could be varied based on mechanisms of their actions for lowering glucose levels including the inhibition of glucose absorption, improvement in insulin resistance and pancreatic functions (Chang *et al.,* 2013)

Quercetin isolated from the aqueous extract of *Matricaria recutita* has shown high inhibitory effects against glucosidase as yeast α-glucosidase, rat intestinal sucrase, and amylase with IC_{50} values as 8.86 μg/mL, 216 μmol/L, and 71 μmol/L respectively (Yin *et al.,* 2014). Mahanine obtained from the fruit pulp of *Murraya koenigii* showed α-glucosidase inhibitory activity as 21.4 ± 0.4 μmol/L compared with acarbose (IC_{50} = 15.2 ± 0.6 μmol/L) (Uvarani *et al.,* 2014). Furthermore, mangiferin (IC_{50} = 299.7 ± 42.3 μmol/L) was isolated from 70% aqueous ethanolic leaf extracts of *Aquilaria sinensis* and showed significant α-glucosidase inhibitory activity than acarbose (IC_{50} = 576.2 ± 58.5 μmol/L) (Feng *et al.,* 2011).

The major steps in the discovery of bioactive compounds from plants are solvent extraction, bioassays, isolation, characterization, toxicological evaluation, preclinical and clinical investigation of isolated bioactive compounds (Sasidharan *et al.,* 2011). Table 2 summarizes some common antidiabetic compounds that have been isolated from medicinal plants.

Polyherbal formulations for the management of diabetes mellitus

Medicinal plants with ethnomedicinal value are currently being screened for their therapeutic potential. Herb-herb combinations are basically found in polyherbal therapy and have been used in Ayurvedic medicine for thousands years (Che *et al.,* 2013). In the Ayurvedic literature 'Sarangdhar Samhita', the concept of polyherbalism and combined extracts of plants are chosen rather than individual ones for the treatment of diabetes mellitus in the traditional system of medicine (Parasuraman *et al.,* 2014). The Unani medicine has also achieved global acceptance due to the amazing clinical efficiency of the polyherbal formulations (Shailajan, 2015). In the majority of traditional systems, diabetes has been successfully managed by the polyherbal mixtures instead of a single herb because of the powerful synergism and less side effects (Yuan *et al.,* 2017). Combinations often lead to promising effects in the management of diseases over a single drug. Naturally occurring herbs and herbal ingredients are organized into certain formulas that offer potential interactions such as mutual enhancement, mutual assistance, mutual restraint and mutual antagonism (Alabi *et al.,* 2017). Many scientific studies have discovered that polyherbal mixtures produce a greater effect, as compared to individual plant extracts. Combined plant extracts also focus on multiple targets at the same time to provide greater effectiveness (Briskin, 2000). In the preparation of polyherbal mixtures, the extent of individual plants used is less in achieving desirable pharmacological action than in a single herbal preparation. Hence, it reduces the risk of harmful side-effects. In addition, polyherbal formulations also prevent the need to take more than one different single herbal formulation at a time. Therefore, all these benefits has led to the popularity of polyherbal mixtures among patients with diabetes. Many researchers have studied polyherbal mixtures in order to evaluate their effectiveness in acute and long term interventions. These studies have revealed that combined plant mixtures have a wide therapeutic range due to the presence of different phytochemicals. Most of the polyherbal mixtures have shown effectiveness even at low or high doses without any toxic effects (Parasuraman

et al., 2014). A summary of recent studies on polyherbal formulation used in the management of diabetes mellitus is shown in Table 3.

Table 2: Reported antidiabetic active compounds isolated from medicinal plants.

Plant	Used part	Active compound	Extract	Mode of study	References
Acacia pennata	Shoot tips	Polyphenols, caffeic acid	Aqueous	In vitro	Wongsa *et al.,* 2012
Bauhinia forficata	Leaves, flower	Kaempferol-3-neohesperidoside	Ethanolic	Rat soleus muscle	Brahmachari, 2011
Capparis moonii	Fruits	Gallotannins	Ethanolic	L 6 cells	Kanaujia *et al.,* 2010
Curcuma longa	Rhizome	Curcumin, demethoxycurcumin, bisdemethoxycurcumin, ar-turmerone	Ethanolic	Diabetic mice and in vitro	Kuroda *et al.,* 2005
Eleutherine americana	Bulb	Eleutherinoside A	Methanol Ethanol	Compound isolation	Ieyama *et al.,* 2011
Macaran gatanarius	Seeds	Ellagitannins (mallotinic acid, corilagin, chebulagic acid, macatannins A and B)	Ethanol	Compound isolation	Gunawan-Puteri and Kawabata, 2010
Murraya koenigii	Leaves	Mahanibine	Petroleum ether	Diabetic rats	Dinesh kumar *et al.,* 2010
Piper retrofractum	*Fruits*	*Piperidine alkaloids: piperine, pipernonaline, dehydropipernonaline*	Ethanolic	*3T3-L1 adipocytes*	Kim *et al*., 2011
Salacia oblonga	Root, stem, leaves	Salacinol, kotalanol, mangiferin	Aqueous	Compound isolation,	Muraoka *et al.,* 2011
Swertia punicea	Whole plant	Methylswertianin, bellidifolin	Ethanolic	Diabetic mice	Tian *et al.,* 2010
Syzygium cumini	Leaves, seeds	Mycaminose	Ethanolic	Diabetic rats	Kumar *et al.,* 2013

Table 3: A list of recently scrutinized polyherbal formulations.

Formulation with scientific names	Scientific evaluation	Outcome of the study	Reference
Alstonia congensis, Stachytarpheta angustifolia, Xylopia aethiopica	alloxan-induceddiabetic rats	Potent hypoglycaemic activity and beneficial effects on cardiovascular risk factors	Ogbonnia *et al.,* 2010
Achillea millefolium , Agathosma betulina, Salvia officinalis, Taraxacum officinalis, Thymus vulgaris, Trigonella foenum-graecum, Urtica urens	*In vitro* study	strong antioxidant and antidiabetic activity	Paddy *et al.,* 2015
Allium sativum, Cinnamomum zeylanicum, Citrullus colocynthis, Juglans regia, Nigella sativa, Olea europaea, Punica granatum, Salvia officinalis, Teucrium polium,Trigonella foenum, Urtica dioica, Vaccinium arctostaphylos	Streptozotocin induced diabetic rats	Beneficial effects on blood glucose and lipid profile and has a potential to be used as a dietary supplement for the management of diabetes	Ghorbani *et al.,* 2013
Allium sativum, Zingiber officinale, Capsicum frutescens	alloxan-induced diabetic rats	Recommended for the treatment of diabetes	Otunola *et al.,* 2015
Glycosmis pentaphylla, Tridax procumbens, Mangifera indica	Streptocotocin induced diabetic rats	significant antidiabetic activity	Petchi *et al.,* 2014
Eugenia jambolana, Gymnema sylvestre, Momordica charantia and Andrographis paniculata, Myristica fragrans	Streptozotocin induced diabetic rats	Significantly reduced blood glucose level	Nagja *et al.,* 2017

Toxicity of medicinal plants and polyherbal mixtures

Toxicology is a branch of science that deals with toxic substances and their effects. Toxicological studies are very important for the development of new safe drugs and for the extension of the therapeutic potential of existing drugs (Parasuraman, 2011). Although medicinal plants play a significant role in the treatment of diseases, many unsafe and fatal side effects have also been reported (Ekor, 2014). These toxic effects might be due to allergic reactions, effects from impurities and interactions with drugs and other herbs (Hussain, 2011). The Organization for Economic Co-operation and Development (OECD) and the International Conference on Harmonization (ICH) have established the guidelines for toxicity studies of pharmacological substances including medicinal plant extracts, herbal mixtures and for isolated compounds (Kiani *et al.,* 2018). Toxicological studies determines whether the plant extract can be accepted for clinical use or not. Even though many phytochemicals are commonly used for health benefits, some of them have been reported as toxic substances and may be present in food or herbal remedies. Arseculeratne and co-workers (1985) have reported some Sri Lankan medicinal plants which are popular in Ayurvedic medicine exerted significant toxic effects such as *Terminalia chebula*. However, there are many antidiabetic plants extracts which have been documented as toxic free extracts with recent scientific investigations such as *Coccinia grandis* (Attanayake *et al.,* 2013b). Table 4 describes toxicological studies conducted on medicinal plants with potent antidiabetic activity.

CONCLUSIONS

In the present review we described the traditional antidiabetic herbal medicines with an emphasis on scientific investigations conducted on antidiabetic medicinal plants, polypherbal mixtures, isolated compounds and their associated toxicities. Herbal medicines are used by a large number of patients with diabetes mellitus since ancient times. The indigenous knowledge on herbal medicines can be successfully blended with modern scientific knowledge to develop antidiabetic agents that can be used in the management of diabetes mellitus. The major hindrance in the amalgamation of medicinal plants with modern therapeutic applications is lack of scientific and clinical data proving their efficacy and safety. Many investigations have been carried out to scrutinize the therapeutic benefits of medicinal plants, and polyherbal mixtures used in different traditional medicine systems. However, a considerable number of medicinal plants used in traditional medicines have not been investigated yet. Therefore, there is a crucial need to conduct scientific investigations to scrutinize the therapeutic potency of medicinal plant extracts and polyherbal mixtures in clinical practice, elucidate the antidiabetic principle(s), and to isolate antidiabetic compounds in the near future.

Table 4: Reported toxic effect of plants which are used in traditional medicine.

Plant	Ethanobotanical use	Used plant part	Solvent	Experimental period	Type of toxicity	Reference
Aframomum melegueta	Stomachache, diarrhea	Seed	Ethanol	Sub chronic (28 days)	Liver	Ilic *et al.,* 2010
Anacardium occidentale	Diabetes mellitus	Leaves	Hexane	Acute (7 days), Chronic (56 days)	Liver and Kidney	Tedong *et al.,* 2007
Cylicodiscus gabunensis	Gastrointestinal disorders	Stem bark	Ethyl acetate	Acute (7 days), sub-acute (6 weeks)	Liver, Kidney and Lungs	Mabeku *et al.,* 2007
Drimysan gustifolia	antiulcer and antiinflammatory	Leaves	Ethanol	Acute (48 hours)	Behavioral changes	Gomes *et al.,* 2013
Galega officinalis	Antidiabetic	Aerial parts	Ethanol	Sub chronic (90 days)	Liver and Lungs	Rasekh *et al.,* 2008
Mammea africanna	Hypercholesterolaemia	Stem bark	Water	Acute (48 hours), sub-acute (21 days)	Liver	Antia *et al.,* 2006
Poygala fruticos	Chronic ulcer	Leaves	Water	Acute (14 days), Sub chronic (31 days)	anti-haemopoietic, hepatotoxic and nephrotoxic	Mukinda and Eagles, 2010

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DECLARATION OF CONFLICT OF INTEREST

The authors declare that no conflicts of interest.

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