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Medicinal plants used in the traditional management of diabetes and its sequelae in Central America: a review

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Abstract

Ethnopharmacological relevance

Globally 387 million people currently have diabetes and it is projected that this condition will be the 7th leading cause of death worldwide by 2030. As of 2012, its total prevalence in Central America (8.5%) was greater than the prevalence in most Latin American countries and the population of this region widely use herbal medicine. The aim of this study is to review the medicinal plants used to treat diabetes and its sequelae in seven Central American countries: Belize, Costa Rica, El Salvador, Guatemala, Honduras, Nicaragua and Panama.

Materials and Methods

We conducted a literature review and extracted from primary sources the plant use reports in traditional remedies that matched one of the following disease categories: diabetes mellitus, kidney disease, urinary problems, skin diseases and infections, cardiovascular disease, sexual dysfunctions, visual loss, and nerve damage. Use reports were entered in a database and data were analysed in terms of the highest number of use reports for diabetes management and for the different sequelae.

We also examined the scientific evidence that might support the local uses of the most reported species.

Results

Out of 535 identified species used to manage diabetes and its sequelae, 104 species are used to manage diabetes and we found *in vitro* and *in vivo* preclinical experimental evidence of hypoglycaemic effect for 16 of the 20 species reported by at least two sources. However, only seven of these species are reported in more than 3 studies: *Momordica charantia* L., *Neurolaena lobata* (L.) R. Br. ex Cass., *Tecoma stans* (L.) Juss. ex Kunth, *Persea americana* Mill., *Psidium guajava* L., *Anacardium occidentale* L. and *Hamelia patens* Jacq. Several of the species that are used to manage diabetes in Central America are also used to treat conditions that may arise as its consequence such as kidney disease, urinary problems and skin conditions.

Conclusion

This review provides an overview of the medicinal plants used to manage diabetes and its sequelae in Central America and of the current scientific knowledge that might explain their traditional use. In Central America a large number of medicinal plants are used to treat this condition and its sequelae, although relatively few species are widely used across the region. For the species used to manage diabetes, there is variation in the availability and quality of pharmacological, chemical and clinical studies to explain traditional use.

Keywords

Diabetes ; Central America ; Medicinal plants ; Ecosystem services ; Traditional medicine ; Hypoglycaemic

Chemical compounds studied in this article

Bixin (PubChem CID: 5281226); Chlorogenic acid (PubChem CID: 1794427); Guaijaverin (PubChem CID: 44259215); Kaempferol 3-*O*-gentiobioside (PubChem CID: 9960512); Peltatoside (PubChem CID: 5484066); Quassin (PubChem CID: 65571); Quercetin (PubChem CID: 5280343); Rhoifolin (PubChem CID: 5282150); Tecomine (PubChem CID: 442553); Vindoline (PubChem CID: 260535)
More information is available at: http://www.elsevier.com/PubChem

Abbreviations

AMPK: AMP-activated protein kinase; IRS-1: insulin receptor substrate-1; NADPH: nicotinamide adenine dinucleotide phosphate; PKB/Akt: protein kinase B; PPARγ: peroxisome proliferator-activated receptor γ; PTP-1B: protein-tyrosine phosphatase 1B; RCT: randomised controlled trial

1. Introduction

Diabetes mellitus is a group of metabolic diseases, characterised by high blood glucose levels (hyperglycaemia) that occurs when there is insufficient insulin secretion from the pancreas, or there are defects in its action, or both. The WHO defines diabetes as having a fasting plasma glucose value

≥ 7.0 mmol/L (126 mg/dl) or being on medication for raised blood glucose (WHO, 2010). The majority of diabetes cases fall into two broad categories: type 1 diabetes (T1D), previously known as insulin-dependent, or juvenile onset diabetes, where there is deficient insulin production; and type 2 diabetes (T2D), previously known as non-insulin dependent or adult-onset diabetes, which accounts for 90% of all diabetes cases, and results from the body's ineffective use of insulin (American Diabetes Association, 2004; WHO, 2015). Although previously only seen in adults, T2D is now occurring in children. There are other categories of diabetes, including gestational diabetes and rarer forms of genetic or acquired diabetes (WHO 2015).

According to the International Diabetes Federation, globally 387 million people currently have diabetes (IDF, 2014), with 80% of adult deaths from diabetes occurring in low and middle income countries (IDF, 2014; WHO, 2015). It is projected that diabetes will be the 7th leading cause of death worldwide by 2030 (WHO, 2015). By 2035, the number of diabetes cases worldwide is expected to increase to 592 million. The number of people with diabetes in the South and Central America Region (SACA) is projected to increase by 60% by 2035, with an average prevalence of diabetes expected to reach 9.8% (Aschner et al., 2014; IDF, 2014). The top five countries with the highest prevalence in 2013 in the SACA Region include two countries in the Caribbean Islands and three countries from Central America: Nicaragua (12.45%), Guatemala (10.87%), and El Salvador (10.50%). A 2012 epidemiologic study also found that the total prevalence of diabetes of 8.5% in the combined Central America sample studied was greater than the prevalence in most Latin American countries. Since the population of Central America is relatively young, the future burden of the disease in the next decades is likely to increase substantially (Barcelo et al., 2012).

The indigenous populations in this region are particularly at risk from diabetes, resulting from marginalisation and lack of access to care and prevention, in addition to dramatic lifestyle changes, including nutrition transition to a diet high in refined carbohydrates (Aschner et al., 2014). Studies have shown that globally, indigenous populations suffer disproportionately from T2D and related complications, regardless of their geographic region (Ferrier et al., 2014; Naqshbandi et al., 2008).

In addition to risk of death from hyperglycaemic crisis, chronic hyperglycaemia from diabetes can lead to many long term health issues. These sequelae include: cardiovascular disease (CD), and an increased risk of heart attack or stroke; chronic kidney disease (KD) leading to end-stage renal disease; urinary problems (UP); peripheral neuropathy (nerve damage, ND); skin infections (SI), especially foot ulcers, that are difficult to heal, with the eventual need for lower-extremity amputation; retinopathy leading to vision loss (VL); and sexual dysfunction (SD). Over 70% of people with T2D may die from cardiovascular disease (Laakso, 2010). Chronic kidney disease, mainly the result of diabetes and hypertension, is the fastest growing non-communicable disease. There are few medicines available to specifically treat diabetic kidney disease. Globally, median years of life lost to chronic kidney disease rose by 90% between 1997 and 2013, compared with a 67% rise in years of life lost to diabetes (The Lancet Diabetes & Endocrinology, 2015).

Compared to people who do not have diabetes, people with diabetes require at least two to three times the health-care resources, and may account for up to 15% of national health care budgets (WHO, 2010). Clearly, diabetes is both a huge health and economic burden globally, and notably for low and middle income countries including those in Central America.

In this paper we present the results of a review of medicinal plants used to treat diabetes and its sequelae in seven Central American countries (Belize, Costa Rica, El Salvador, Guatemala, Honduras, Nicaragua and Panama). The data are analysed in terms of the highest number of use reports for the management of diabetes and for each of the different sequelae. The regional approach we have taken provides a useful overview and indication of which plants may provide benefit in the management of diabetes and its sequelae. Whilst the aim of this review is to capture use data for species indicative of having relevance to diabetes in the selected Central American countries, we also explore the scientific evidence that appears to support the local uses of the most reported species. It is beyond the scope of this review to extensively discuss the available data on the pharmacological activities and clinical studies for all of the recorded species. However, where promising data are available and there is knowledge of the phytochemical constituents that might aid our understanding of the scientific basis for traditional use (and potential use), these are briefly discussed.

2. Methods

For the purpose of this review we defined Central America as the region including Belize, Guatemala, Honduras, El Salvador, Nicaragua, Costa Rica and Panama. We conducted a literature review by searching for combination of keywords such as the name of the country and "medicinal plants", "ethnobotany", "ethnopharmacology", "ethnomedicine", and "herbal medicine" in the databases SCOPUS, Web of Science, Google Scholar, and Pubmed. The search was conducted using both English and Spanish keywords. We also conducted such searches on single journals such as Journal of Ethnopharmacology, and the Journal of Ethnobiology and Ethnomedicine. To cover some of the gaps in the literature found during these searches, we conducted a literature research of books held at the library of the Royal Botanic Gardens Kew, including books published in English, Spanish and French. We included in our review only studies publishing primary data validated by the collection of voucher specimens to avoid double counting (Leonti, 2011) use reports generated from the same research. This included 24 journal papers, 1 conference proceeding, 1 PhD thesis, and 6 books (total 32 sources used). When sources included both primary and secondary data, such as for example in Balick and Arvigo (2015), and these were clearly differentiated in the text, then we included only the primary data in our database.

From the literature included in this study we extracted the use-reports that matched one of the following disease categories: diabetes mellitus, kidney disease, urinary problems, skin diseases and infections, cardiovascular disease, sexual dysfunctions, visual loss, and nerve damage. These use reports were entered in a bespoke Access relational database [see supplementary material in (Giovannini et al., submitted)], including the disease category, the reference, the name of the species, and how it is used. We excluded from our database taxa that were not identified at species level.

Name validation

Scientific names of plants that met our criteria for assessment in this review, along with associated data, were compiled in a bespoke Access relational database. The majority of these names were checked manually against The Plant List Version 1.1 (TPL) at point of entry. TPL was created through merging of Kew's various name datasets (both published and unpublished), along with major datasets supplied by Kew's partners, including Missouri Botanical Garden (US). As TPL was synthesised automatically, rather than compiled by human specialists, the reliability of TPL is variable, so records are assigned one of three confidence levels. Of the 607 scientific plant names checked we found 6% with a low confidence level and the remaining 94% with a high or medium confidence level. On completion of data entry, the entire dataset of scientific plant names was evaluated automatically against TPL for precision, confidence level, taxonomic currency, and synonymy. Names that did not match due to typographic errors were found using 'fuzzy' searches, setting the Levenshtein distance to 2. After name validation was carried out the database included 537plant taxa (for a total of 535 plant species, as 2 taxa are infraspecific), and 1055 use reports within the categories included in this review after excluding secondary data and taxa that were not identified at species level.

3. Results and discussion

3.1 Plant families with species used to treat diabetes and its sequelae in Central America

The families with more recorded species to manage diabetes mellitus in Central America are Asteraceae (7 species), Fabaceae (7 species), Rubiaceae (6 species), Euphorbiaceae (6 species), Bignoniaceae (5 species), Myrtaceae (5 species), Rutaceae (5 species), Amaranthaceae (4 species), and Solanaceae (3 species). Some of the known phytochemical classes that occur in these families and how this knowledge might contribute to our understanding of the relevance of these particular families to diabetes are summarised below.

Of 656 flowering plants identified as associated with traditional uses relevant to diabetes in a previous study, a high proportion of the 437 genera, representing 111 families, were from the asterids and rosids (Simmonds and Howes, 2006). There is chemical diversity amongst the rosids, and members of the Fabaceae are reported to include flavonoids, alkaloids and triterpene saponins amongst their constituents (Leonti et al., 2003; Simmonds and Howes, 2006). Simmonds and Howes (2006) identified 81 species within the Fabaceae with reported hypoglycaemic activity (Simmonds and Howes 2006). Flavonoids from the Fabaceae have been widely studied and include those with mechanistic effects relevant to diabetes, as reviewed in Simmonds and Howes (2006).

It has been estimated that almost 50% of the plant-derived natural products that are pharmaceutically and biologically significant are alkaloids (Cordell et al., 2001). Therefore knowledge of their taxonomic distribution can assist with our understanding of the traditional uses of alkaloid-containing species as medicines. Similarly to the Fabaceae, members of the Rubiaceae also include many alkaloid containing species; in the Rubiaceae these include those of the monoterpenoid-indole class; other phytochemicals reported for this family include iridoids and anthraquinones (De Kuca et al., 2014; Han et al., 2001). Solanaceae members contain a wide range of biologically active alkaloids, including tropane, pyrrolidine, glycoalkaloid and steroidal alkaloid classes (Cadenas et al., 2015; Griffin and Lin, 2000; Pomilo et al., 2008). Although often relevant for biological activities with therapeutic effects, alkaloids may also be associated with toxic effects, which should be considered when also evaluating traditional uses and the traditional methods of preparation. Members of the Euphorbiaceae also contain alkaloids (including the tropane class), in addition to diterpenes and polyphenols, whilst some members also contain triterpenes and cyanogenic glycosides (Griffin and Lin, 2000; Leonti et al., 2003; Tanaka and Matsunaga, 1999). Polyphenols have been linked to beneficial effects for the management of diabetes such as reduced absorption of dietary carbohydrate, regulation of carbohydrate metabolism and stimulation of insulin secretion (Bahadoran et al., 2013). Intake of polyphenols is also associated with favourable effects on risk factors for type 2 diabetes (Simmonds and Howes, in press).

Asteraceae and Fabaceae are both large plant families containing a wide variety of phytochemical classes. Members of the Asteraceae are reported to contains polyacetylenes, sesquiterpene lactones, monoterpenes, diterpenes, phenolic compounds (including flavonoids) and alkaloids (including those of the pyrrolizidine class); the latter have often be associated with hepatotoxicity (Heinrich et al., 1998; Leonti et al., 2003; Roeder, 2000). The bitter phytochemicals present in some

Asteraceae have been suggested to be linked with increased experimentation from local people linking bitter taste to medical properties (Casagrande 2002; Heinrich et al., 1998); this is especially true when people look for plants to manage diabetes (Giovannini personal communication). Several studies show this plant family is often overrepresented in plant pharmacopoeias (Amiguet et al., 2006; Leonti et al., 2003; Moerman 1996; Thomas et al., 2009). Sesquiterpene lactones, including those from *Neurolaena* species have been associated with anti-inflammatory activity (McKinnon et al., 2014; Walshe-Roussel et al., 2013), although this compound class has not been associated with hypoglycaemic effects in some studies (Davis, 1997) (see section 3.2).

Genera in the Myrtaceae are often associated with volatile oil production, with many species containing monoterpenes as the major volatile oil constituents (Stefanello et al., 2011). Alkaloids are reported less frequently in this family. Members of the Rutaceae also produce volatile oils, alkaloids of various classes, coumarins and triterpenoids (Epifano et al., 2015; Jing et al., 2015). Many plant volatile oils have been associated with antimicrobial effects, including those from members of the Myrtaceae (Stefanello et al., 2011) and Rutaceae (Chintaluri et al., 2015). Antimicrobial effects, due to the volatile oil constituents, might provide some explanation for traditional uses for skin infections. Members of the Amaranthaceae also produce volatile oils, in addition to betalains, phenolic compounds and terpenoids, including triterpene saponins that have been associated with anti-diabetic effects (Mroczek, 2015). Triterpene from various species have been associated with mechanistic effects relevant to diabetes, as reviewed in Simmonds and Howes (2006). Members of the Bignoniaceae have been reported to contain iridoids and phenylpropanoids; both compound classes are reported in *Tecoma* species (De Luca et al., 2014; Guiso et al., 1997). Alkaloids are reported less frequently in this family, although some alkaloids from *Tecoma* species have been associated with hypoglycaemic effects (see section 3.2).

3.2 Plant species used to treat diabetes and its sequelae in Central America

In this section we review our findings at species level and we discuss current scientific evidence that might explain the uses of the most reported plant species to manage diabetes and its sequelae. Table 1 shows the plant species reported in at least two sources as remedies to manage diabetes by the local population and whether these species are reported also to treat some of the sequelae of diabetes such as kidney disease, urinary problems, vision loss, cardiovascular problems, and skin conditions. Table 2 shows the species used to treat skin conditions, Table 3 shows species reported as treatments for kidney disease, and Table 4 shows the species used to treat urinary complaints. Figure 1 shows the species with a high number of use reports for all the disease categories considered in this review. We do not present tables for the species reported as treatments for cardiovascular disease, vision loss and sexual dysfunction as we found that relatively few species were reported for these use categories.

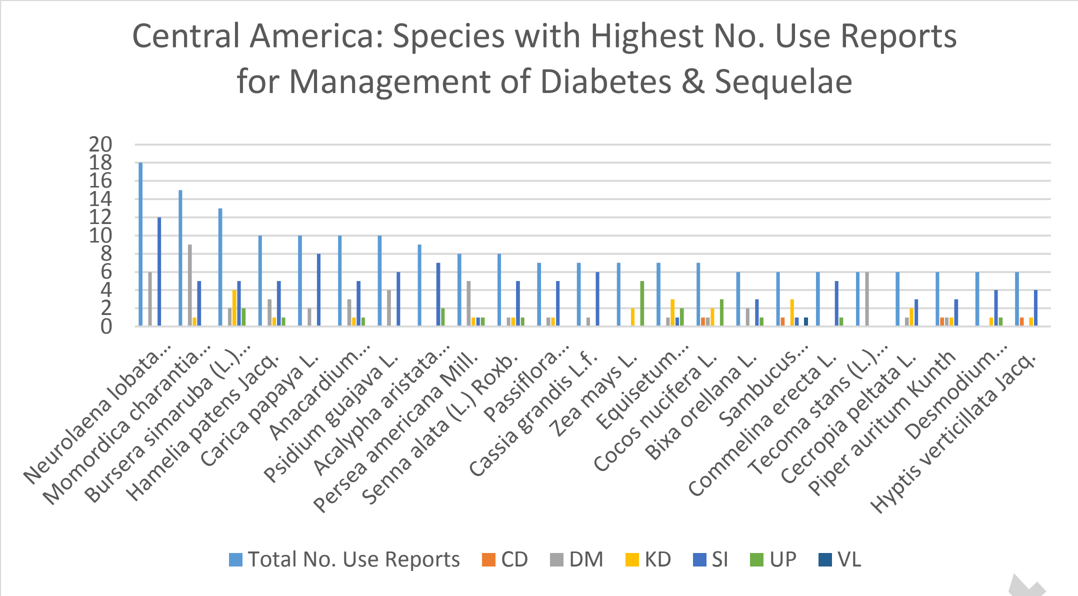

Figure 1. Species with highest number of use reports for the management of diabetes and the treatment of its sequelae. CD= cardiovascular disease, DM=diabetes, KD=kidney disease, SI=skin conditions, VL=vision loss.

Out of the 104 species that we found are used to manage diabetes in Central America, the species with at least 3 use reports were: *Momordica charantia* L., *Neurolaena lobata* (L.) R. Br. ex Cass., *Tecoma stans* (L.) Juss. ex Kunth, *Persea americana* Mill., *Psidium guajava* L., *Anacardium occidentale* L. and *Hamelia patens* Jacq.

Momordica charantia L. is grown and is used to treat diabetes by indigenous and local communities in tropical areas of Asia, South-America, Central America, Mexico, India, Africa, and the Caribbean (Grover and Yadav 2004; Leung et al., 2009). Its hypoglycaemic properties have been shown in several animal studies, although few trials on humans have been conducted and there is a lack of randomised controlled trials (RCTs) that demonstrate its efficacy; there are more data for the fruits compared to other plant parts (Ooi et al., 2010; Yeh et al., 2003). We found that this species was reported independently as a treatment for diabetes in 9 ethnobotanical studies conducted in Central America and the leaf was the most commonly reported plant part used (in 7 out of 9 of reports). Pharmacological and phytochemical studies have focused on the fruits of this species (which are used in other traditional practices of medicine) and have revealed that cucurbitane-type triterpenoids in particular show mechanistic effects relevant to diabetes (Chang et al., 2015; Nhiem et al., 2010; Tan et al., 2008). Interestingly, the stems of this species also contain triterpenoids, including 3β,7β,25-trihydroxycucurbita-5,23(*E*)-dien-19-al, which was previously isolated from the fruits and hypoglycaemic when tested in alloxan-induced diabetic mice (Cheng et al., 2008). The stem triterpenoids [including 3β,7β,25-trihydroxycucurbita-5,23(*E*)-dien-19-al] also modulated insulin resistance in vitro, which was associated with activation of AMPK, enhancing tyrosine phosphorylation of IRS-1 to modulate the insulin signalling pathway (Cheng et al., 2008). Charantin (a mixture of steroidal saponins) from the fruits of *M. charantia* is reported as hypoglycaemic (Krawinkel and Keding, 2006), yet it occurs at higher concentrations in the leaves (El-Said and Al-Barak, 2011). Thus, the triterpenoids and charantin that occur in the leaves (the most commonly reported plant part in this study) and stems of *M. charantia* appear to provide some scientific basis for the traditional use for diabetes.
We also found 5 independent reports of *M. charantia* to treat skin conditions in Central America. Indeed, several studies associate this species with broad-spectrum anti-microbial activity (Ooi et al.,

2010; Grover and Yadav, 2004), which could be linked to some of its traditional uses. However, the fruit extracts have shown more potent antibacterial activity than leaf extracts (Supraja and Usha, 2013).

Neurolaena lobata (L.) R. Br. ex Cass is a herb found in Mexico, Central America, the Caribbean, and North South-America (GBIF, 2015a). We found six reports of the use of this species to manage diabetes in Central America (Balick and Arvigo, 2015; Barrett, 1994; Cruz and Andrade-Cetto, 2015; Ferrier, 2014; Girón et al., 1991; Pöll 1997). The traditional use of *N. lobata* to manage diabetes has been reported in Mexico and in the Caribbean (Andrade-Cetto and Heinrich, 2005; Soumyanath, 2005) and its leaf extracts significantly decrease blood glucose in mice (Gupta et al., 1984). However, no specific antidiabetic compounds have been isolated from this species to date, and RCTs are also lacking. Our review shows that *N. lobata* is also widely used in Central America to treat skin conditions. The results of animal studies appear to support the healing activity of this species in cutaneous wounds (Nayak et al., 2014) and it also has antimicrobial activity (Nayak et al., 2014). Extracts of *N. lobata* showed anti-ulcerogenic and anti-nociceptive effects (Gracioso et al., 2000; Gracioso et al., 1998). Furthermore, other studies revealed that extracts from this species have anti-inflammatory activity and several sesquiterpene lactones have been identified that mediate this effect (McKinnon et al., 2014; Walshe-Roussel et al., 2013).

Tecoma stans (L.) Juss. ex Kunth, a native of the Americas, is a shrub or small tree widely distributed in the tropics and subtropics (Pelton, 1964). It is used in Mexico and Central America to manage diabetes and treat urinary disorders (Aguilar-Santamaría et al., 2009). We found six reports of its use in the management of diabetes in Guatemala and in El Salvador (Cruz and Andrade-Cetto, 2015; Girón et al., 1991; Gonzalez-Ayala, 1994; MacVean, 2006; Nicolas, 1999; Pöll, 1997). Accordingly, its extracts have hypoglycaemic activity in animal models of diabetes (Román-Ramos et al., 1990). Leaf extracts inhibit intestinal α-glucosidase, modulate postprandial hyperglycaemia and reduce triglycerides and cholesterol *in vivo* (Aguilar-Santamaría et al., 2009), which may provide some scientific explanation for the traditional use. Studies report the alkaloid tecomine from the leaves of this species to be hypoglycaemic *in vivo*, although it has low stability (Hammouda and Khalafallah, 1971). Other studies concluded that alkaloids, including tecomine and tecostanine, were not hypoglycaemic *in vivo* (Costantino et al., 2003). Therefore, traditional preparations would need to be further evaluated to determine the stability of these alkaloids and their role in explaining the scientific basis for the use of this in diabetes.

We found 5 reports of uses of *Persea americana* Mill. to manage diabetes in Central America, in most cases the plant part used was the leaf but there are also reports of the use of the bark and the seed (Balick and Arvigo 2015; Coe and Anderson, 1999; Coe and Anderson 1996; Cruz and Andrade-Cetto 2015; Gonzalez-Ayala, 1994). We also found reports of the use of *P. americana* to treat kidney disease and urinary problems. Animal studies showed that extracts of *P. americana* have hypoglycaemic properties, improve kidney function and blood pressure, and reduce cholesterol and triglycerides levels (Antia et al., 2005; Brai et al., 2007; Ezejiofor et al., 2013; Gondwe et al., 2008; Imafidon and Amaechina 2010). A hydroalcoholic extract of the leaves was suggested to be hypoglycaemic *in vivo*, via regulation of glucose uptake in liver and muscles via PKB/Akt activation (Lima et al., 2012). Preliminary clinical trials showed that dietary consumption of this species might maintain cardiovascular health (Dreher and Davenport, 2013) due to its antihypercholesterolaemic and antihyperlipidaemic activity (Lim, 2012), although RCTs specifically investigating the anti-diabetic properties of this species are lacking.

Psidium guajava L. is a small tree used medicinally in most tropical and subtropical areas. We found 4 studies reporting its use to manage diabetes in Guatemala (Cruz and Andrade-Cetto, 2015; Girón et al., 1991; MacVean 2006; Pöll, 1997). The use of this species to manage diabetes has also been reported in South Africa and in the Caribbean (Gutiérrez et al., 2008). Studies conducted on animals have shown that extracts from *P. guajava* lower blood glucose (Mukhtar et al., 2006; Mukhtar et al., 2004; Oh et al., 2005; Ojewole 2005; Ruiz et al., 2011; Shen et al., 2008). This species is also an anti-LDL glycative agent, which make it potentially useful in the prevention of cardiovascular and neurodegenerative diseases (Gutiérrez et al., 2008). Phenolic compounds, including gallic acid, catechin and quercetin, are considered to contribute to the anti-glycation effects of leaf extracts (Wu et al., 2009). Furthermore, the flavonols quercetin, kaempferol and myricetin showed inhibitory activities against sucrase, maltase and α-amylase in vitro (Wang et al., 2010). Flavonol glycosides (peltatoside, hyperoside, isoquercitrin and guaijaverin in particular) from the leaves of this species also inhibited dipeptidyl peptidase IV, a key enzyme for blood glucose homeostasis (Eidenberger et al., 2013), which might provide some scientific explanation for the traditional use of the leaves for diabetes.

Our results suggest that in Central America this species is also widely used for skin conditions, with six studies conducted in Belize, Nicaragua and Guatemala reporting the use of this species for this use category. This could be related to the reported antimicrobial, analgesic and anti-inflammatory properties of *P. guajava* (Gutiérrez et al., 2008). Known antibacterial compounds in the leaves include the flavonol glycoside guaijaverin (Prabu et al., 2006) and the benzophenone glycoside, guajaphenone A (Ukwueze at al., 2015), whilst quercetin and the 3-*O*-arabinoside showed anti-quorum sensing activity (Vasavi et al., 2014). Thus, there appears to be some scientific evidence to explain the use of the leaves of this species in particular for both internal and external use. The range of biological activities demonstrated to date for extracts and individual constituents suggest that 'polyvalency' is important for the reputed benefits of this species for diabetes, such that several different constituents may act via different modes of action to produce an overall effect on diabetes parameters.

Anacardium occidentale L., known as cashew tree, is widely distributed in Central America and in tropical South America but also widely cultivated in some parts of Africa and in Asia (GBIF 2015b). Several Central American ethnobotanical studies report that the bark and leaf of this species is used to manage diabetes mellitus (Duke 1986; Cruz and Andrade-Cetto 2015; Gupta et al., 1979), skin conditions (Barrett 1994; Coe 2008; Coe and Anderson, 1999; Coe and Anderson, 1996; Coe et al., 1997), kidney disease and urinary problems (Gonzalez-Ayala, 1994). Animal studies on extracts of *A. occidentale* showed a hypoglycaemic effect (Esimone et al., 2001; Ojewole, 2003; Olatunji et al., 2005; Sokeng et al., 2001), in addition to anti-inflammatory activity (Mota et al., 1985). Tedong et al. (2006) showed that an extract of *A. occidentale* has a renal protective effect on streptozotocin induced diabetic rats. It is suggested that stigmast-4-en-3-ol and stigmast-4-en-3-one contribute to the hypoglycaemic effect of bark extracts, since these steroidal compounds were associated with producing hypoglycaemia *in vivo* (Alexander-Lindo et al., 2004).

Hamelia patens Jacq. is a native shrub of American subtropics and tropics. The use of a decoction of the leaves of *H. patens* to manage diabetes was reported in 3 studies conducted in Belize, Guatemala and El Salvador (Balick and Arvigo, 2015; Cruz and Andrade-Cetto, 2015; Gonzalez-Ayala, 1994). There is a lack of studies on *H. patens* potential antidiabetic properties, however one study suggests that the extract of this species is hypoglycaemic (Pandurangan et al., 2013). An ethanol extract of the leaves was antinociceptive *in vivo* (Alonso-Castro et al., 2015), which might suggest a rationale for traditional use to alleviate symptoms, rather than target hyperglycaemia. We found that this species is also widely used to treat skin conditions with 5 studies from Belize, Nicaragua and El Salvador documenting uses such as such as skin infections, rashes and sores. Previous studies showed that extracts of this species have anti-microbial (Camporese et al., 2003), anti-inflammatory (Sosa et al., 2002) and wound healing activities (Gomez-Beloz et al., 2003). More studies are needed to understand more about any pharmacological basis for the traditional use for diabetes and the constituents that may mediate any relevant mechanistic effects.

Bursera simaruba (L.) Sarg is a tree growing in Mexico, Central America, the Caribbean, and Northern South America. We found 2 studies, both from Belize, reporting the use of *B. simaruba* in the management of diabetes mellitus (Balick and Arvigo, 2015; Ferrier, 2014). Interestingly, this species is also used in Mexico to manage diabetes (Andrade-Cetto and Heinrich, 2005) and it is widely used in Central America to treat skin conditions, kidney disease and urinary problems (Balick and Arvigo, 2015; Coe, 2008; Coe et al., 1997; Coe and Anderson, 1996; Duke, 1986; Gupta et al., 2005; Kufer et al., 2005; MacVean, 2006). Animal studies showed anti-microbial and anti-inflammatory activity of the extracts (Bork et al., 1996; Camporese et al., 2003; Noguera et al., 2004; Sosa et al., 2002) but there is a lack of studies investigating its anti-diabetic properties. There is also a lack of research on the phytochemical constituents that may mediate effects relevant to diabetes. One study has suggested that methyl-β-peltatin A may contribute to the anti-inflammatory activity of the leaves (Noguera et al., 2004). Considering its use in Mexico and in Central America for the management of diabetes and the treatment of its sequelae, this species is a good candidate for further research to understand more about any scientific basis for its traditional use.

Carica papaya L. is a widely cultivated tropical tree native of the Americas. We found reports for the use of *C. papaya* in the management of diabetes in Belize (Balick and Arvigo, 2015) and Guatemala (Cruz and Andrade-Cetto, 2015). Moreover the use of this species to treat skin conditions was mentioned in eight studies in Central American countries including Belize, Panama, El Salvador and Nicaragua. Pharmacological studies show that extracts of the seeds and leaves of this species have hypoglycaemic, hypolipidaemic and wound healing activities in experimentally induced diabetic rats (Adeneye et al., 2009; Juárez-Rojop et al., 2012; Maniyar and Bhixavatimath, 2012; Nayak et al., 2007; Sasidharan et al., 2011). Although mechanistic effects relevant to diabetes are reported for *C. papaya*, the compounds that mediate these effects have not been widely investigated and more research is needed to understand the constituents that might explain the pharmacological basis for use. Interestingly, Balick and Arvigo (2015) report the use of the root of this species in the management of diabetes in a decoction with *Chamaesyce hypericifolia* (L.) Millsp. and *Capraria biflora* L. or in another mixture with *Euphorbia armourii* Millsp. and wood from *Pinus caribaea* var. *hondurensis*.

Bixa orellana L. is a native shrub from the Americas that is now widely cultivated in tropical and subtropical areas. We found a study conducted in Guatemala (Girón et al., 1991) and one in Belize (Ferrier 2014) reporting its use to manage diabetes. Studies conducted in Nicaragua (Coe, 2008) and Belize (Balick and Arvigo, 2015) also reports its use to treat skin conditions and for urinary problems (Balick and Arvigo, 2015). Studies *in vivo* revealed extracts from its seed can have both hypoglycaemic or hyperglycaemic activity, depending on how the extract is prepared (Morrison et al., 1990; Quanico et al., 2008; Russell et al., 2008) in addition to a hypolipidaemic effect (Ferreira et al., 2013). One study reports the carotenoids bixin and norbixin, from *B. orellana* seeds, to have opposing effects on glycaemia, lipidaemia and oxidative stress in streptozotocin-induced diabetic rats (Roehrs et al., 2014). Thus, more knowledge on the traditional preparations and their differences in chemical constituents might aid our understanding of the scientific basis to explain traditional use for diabetes, to enable direct correlation with, and greater understanding of, the traditional methods of preparation. *B. orellana* extracts are reported to contain a mixture of carotenoids, including β-carotene, which inhibit the expression of NADPH oxidase subunits and increase the expression of antioxidant enzymes in neutrophils in an animal model of diabetes

(Rossoni-Júnior et al., 2012), suggesting potential amelioration of neutrophil dysfunction that can occur in diabetes. A clinical trial showed beneficial effects of an extract of this species administered as an adjunct on type-2 diabetes patients (Herrera-Arellano et al., 2004). However, more RCTs are needed to enable more firm conclusions on efficacy, performed with chemically-characterised extracts that reflect preparations that mediate hypoglycaemic effects (rather than the hyperglycaemic activity reported for some extracts, as described above).

Cecropia obtusifolia Bertol. is a tree growing in tropical forest and found in Mexico and Central America. Its use to manage diabetes was reported in Guatemala (Cruz and Andrade-Cetto, 2015) and in Belize (Balick and Arvigo, 2015). Extracts of this species were found to have a hypoglycaemic effect and Andrade-Cetto (2001) identified chlorogenic acid as one of the active hypoglycaemic compounds in the extract (Andrade-Cetto and Wiedenfeld, 2001). Other constituents that may contribute to the hypoglycaemic effects of extracts, and their specific modes of action, are yet to be determined. Two clinical trials showed beneficial effects of extract of this species, including when administered as an adjunct, in type-2 diabetes patients (Herrera-Arellano et al., 2004; Revilla-Monsalve et al., 2007). Furthermore, Gonzalez-Ayala (1994) reports the use of this species in El Salvador to treat kidney diseases and Coe (2008) reports its use among the Rama of Nicaragua to treat skin conditions. A pharmacological study showed that this species has anti-inflammatory and analgesic properties that could be related to its traditional use (Pérez-Guerrero et al., 2001). Interestingly, we found also a report of the use in Central America of the related *C. peltata* to manage diabetes mellitus (Balick and Arvigo, 2015), to treat kidney diseases and to treat skin conditions. This species is also used in Mexico to manage diabetes (Andrade-Cetto and Heinrich, 2005) and *in vivo* studies showed that its extracts have hypoglycaemic activity (Andrade-Cetto et al., 2007; Nicasio et al., 2005) and would healing properties (Nayak, 2006).

Tridax procumbens (L.) L. is a weed native to the tropical Americas. Animal studies showed that extracts of the leaves and of the whole plant have anti-diabetic and anti-hyperlipidaemic activity (Bhagwat et al., 2008; Pareek et al., 2009; Petchi et al., 2013). A pilot 4-week clinical study revealed that when administered to individuals with type 2 diabetes, an extract of the whole plant of *T. procumbens* (containing carotenoids, flavonoids and other phenolics) lowered blood glucose with no serious adverse effects reported (Desai et al., 2015). We also found a report of its use to treat kidney disease in El Salvador (Gonzalez-Ayala, 1994). This species is used traditionally in Nigeria as a treatment to reduce blood pressure and the findings of *in vivo* studies appear to supports this use (Salahdeen et al., 2004).

Acosmium panamense (Benth.) Yakovlev is a tree naturally distributed in Mexico and in Central America (GBIF, 2015c). We found two sources reporting the use of *A. panamense* to manage diabetes in Belize (Balick and Arvigo, 2015; Ferrier, 2014). The use of this species in the management of diabetes was also reported in Mexico (Andrade-Cetto and Heinrich, 2005) and animal studies on the extracts of its bark showed hypoglycaemic activity (Andrade-Cetto and Wiedenfeld, 2004). Studies to investigate the hypoglycaemic chemical constituents of this species are lacking, although the bark does contain methoxylated quinolizidine alkaloids (Veitch et al., 1997), therefore safety would also need to be evaluated in addition to further studies on efficacy in diabetes.

Quassia amara L. is a shrub growing in Central and South America (GBIF, 2015d). We found reports of its use to manage diabetes in Guatemala (Caceres et al., 1991) and in El Salvador (Gonzalez-Ayala, 1994). The use of *Q. amara* to manage diabetes has also been documented in Suriname (Mans 2012) and among Suriname's migrants in Holland (van Andel and Westers, 2010). Animal studies showed antidiabetic activity of the extracts of this species (Husain et al., 2011; Ferreira et al., 2013), which included the observation of a hypoglycaemic effect with a standardised extract containing quassin, isoquassin and neoquassin (Husain et al., 2011); quassinoids are reported to act as insulin secretagogues (Husain et al., 2011).

Artemisia absinthium L. is an herb native of the Mediterranean region. Animal studies found that extracts from this species have anti-hyperglycaemic activity (Daradka et al., 2014) and glucosidase and lipase inhibitory activities (Ramírez et al., 2012). The compounds responsible for these effects are yet to be investigated, although they are unlikely to be artemisinin derivatives, since these compounds have not been associated with hypoglycaemia (Davis, 1997).

Catharanthus roseus (L.) G. Don is used to manage diabetes in several part of the world. In Central America we found reports of this use in Belize and in El Salvador (Balick and Arvigo, 2015; Gonzalez-Ayala, 1994). Several animal studies showed that extracts from this species have a hypoglycaemic effect (Islam et al., 2009; Jayanthi et al., 2010; Mostofa et al., 2007; Nammi et al., 2003; Natarajan et al., 2012; Rasineni et al., 2010) and they reduce serum cholesterol and triglycerides (Antia et al., 2005). An indole alkaloid, vindogentianine, from the leaves of this species was hypoglycaemic *in vivo*, an effect that was associated with enhanced glucose uptake and PTP-1B inhibition (Tiong et al., 2015). Another alkaloid, vindoline, which occurs in the leaves of this species, improved glucose homeostasis in animal models of diabetes and it protected β-cell function from apoptosis (Yao et al., 2013). These studies appear to provide some scientific basis to explain the traditional use of the leaves of this species for diabetes.

Acrocomia aculeata (Jacq.) Lodd. ex Mart. is a 10-20 m tall palm. Animal studies conducted on this species showed the extract to have a hypoglycaemic effect (Perez et al., 1992) and a new tetrapyrane compound with hypoglycaemic activity was isolated from it (Pérez et al., 1997). Other studies on this species in relation to diabetes are lacking.

Equisetum myriochaetum Schltdl. & Cham. is also widely used in Mexico to manage diabetes and to treat urinary problems (Andrade-Cetto and Heinrich, 2005). Animal studies of extracts of *E. myriochaetum* showed hypoglycaemic activity and the active constituents were suggested to be kaempferol glycosides and a caffeoyl glucoside (Cetto et al., 2000; Revilla et al., 2002).

We found reports of the use of *Hymenaea courbaril* L., a tree found in Central America and South America, to treat kidney disease in Guatemala, Nicaragua and El Salvador (Kufer et al., 2005; Barrett, 1994; Gonzalez-Ayala, 1994). Interestingly, Gupta reports that the infusion of the tea and leaves of *H. courbaril* has hypoglycemic activity (Gupta et al., 1979), although the compounds responsible are unknown.

We found that a decoction of *Pachira aquatica* Aubl is used orally in Central America to treat kidney disease, urinary problems and skin conditions such as rashes and sores (Arnason et al., 1980; Balick and Arvigo, 2015; Coe, 2008; Coe et al., 1997; Coe and Anderson, 1996). Although we did not find any report for the use of *P. aquatica* to manage diabetes in Central America, this use has been reported in at least 3 studies in Mexico (Hernandez-Galicia et al., 2002). Currently, there is a lack of pharmacological and phytochemical studies investigating the anti-diabetic activity of this species.

Similarly, a decoction of *Desmodium adscendens* (Sw.) DC. is used orally in Central America to treat skin conditions, kidney disease and urinary problems. Although we did find any not direct evidence for the use of *D. adscendens* to manage diabetes, *D. gangeticum* (L.) DC. is used in ayurvedic traditional medicine for the management of diabetes and studies showed that this species has antidiabetic activity (Govindarajan et al., 2007). It is possible that other members of the genus *Desmodium*, including *D. adscendens*, could potentially produce mechanistic effects such as hypoglycaemia, thus this genus may be of interest to investigate further, from the ethnobotanical and pharmacological perspectives.

We found 1 report of the use of *Cocos nucifera* L. (coconut) to manage diabetes in Central America (Barrett, 1994) along with reports for its use to treat cardiovascular disease, kidney disease and urinary problems (Balick and Arvigo, 2015; Girón et al., 1991; Gonzalez-Ayala 1994). There is some pharmacological evidence supporting the use of this species to manage diabetes and its sequelae: an extract of *C. nucifera* was anti-hyperglycaemic *in vivo* (Naskar et al., 2011); furthermore, coconut water showed beneficial effects on some biochemical parameters in diabetic rats (Preetha et al., 2013) and consumption of coconut fibre from its flour is reported to decrease the glycaemic index of food (Trinidad et al., 2003).

Girón et al (1991) reports the use of the leaf of *Senna alata* (L.) Roxb. to manage diabetes among the Caribs of Guatemala, and Balick and Arvigo (2015) reports the use of a decoction of the leaves and flowers of this species to treat kidney and urinary complaints in Belize. Moreover, several sources report the use of this species to treat skin infections, rashes and sores in Nicaragua (Coe 2008; Coe et al., 1997; Coe and Anderson, 1999; Coe and Anderson, 1996; Barrett 1994). Among the Miskitu of Nicaragua, the plant is also used to treat hypertension (Coe and Anderson, 1999). Animal studies of an extract of the leaves of this species showed an α-glucosidase inhibitory effect (Varghese et al., 2013) and a hypoglycaemic effect *in vivo* (Palanichamy et al., 1988). The α-glucosidase inhibitory activity of the leaves has been attributed to kaempferol 3-*O*-gentiobioside (Varghese et al., 2013). *Sambucus canadensis* L. is used in Central America to treat kidney disease, urinary problems and skin conditions (Gonzalez-Ayala, 1994; MacVean, 2006; Nicolas 1999). There is a lack of studies supporting the traditional use of this species, except one study that found *in vitro* insulin-like actions of the related *Sambucus nigra* (Gray et al., 2000). Polyphenols from the fruit of the latter species have been associated with hypoglycaemic, hypolipidaemic and antioxidant effects in a rat model of diabetes (Ciocoiu et al., 2009). Extracts from the flowers of *S. nigra*, and the flower constituents α-linolenic acid, linoleic acid and the flavanone naringenin, activate PPARγ and stimulate insulin-dependent glucose uptake, indicating relevance for modulating insulin resistance (Christensen et al., 2010). Other *S. nigra* flower constituents, notably ferulic, *p*-coumaric, caffeic acids, and kaempferol increased glucose uptake *in vitro* and reduced fat accumulation in *Caenorhabditis elegans* (Bhattacharya et al., 2013). Thus, investigations on the constituents of *S. canadensis* would be of interest to determine any mechanistic effects relevant to diabetes and to understand the phytochemicals responsible, enabling direct comparisons of biological properties of these two *Sambucus* species in relation to their traditional uses.

Aloe vera (L.) Burm.f. is a widely used medicinal plant. In Central America we found one report of its use to manage diabetes in El Salvador (Gonzalez-Ayala, 1994) and reports as a treatment for skin conditions, and for kidney disease in Belize and El Salvador (Balick and Arvigo, 2015; Gonzalez-Ayala 1994). This species is also used in Mexico to manage diabetes (Andrade-Cetto and Heinrich, 2005) and animal studies showed its extracts to have hypoglycaemic activity (Kim et al., 2009; Rajasekaran et al., 2005; Rajasekaran et al., 2004) and wound healing activity in diabetic rats (Chithra et al., 1998). Clinical trials concluded that *A. vera* juice is effective in lowering blood sugar and triglycerides in diabetes patients (Bunyapraphatsara et al., 1996; Yongchaiyudha et al., 1996), although more extensive RCTs are needed, which specifically investigate standardised extracts to enable firmer conclusions on efficacy to be determined. The biological activities of *A. vera*, including those relevant to diabetes and its sequelae, have been widely reviewed previously and recent updates on the biological effects and phytochemical constituents are described in Chinchilla et al. (2013).

Eysenhardtia adenostylis Baill. is used among the Cakchiquels in Guatemala to treat diabetes (Cruz and Andrade-Cetto, 2015). We also found reports of its use to treat kidney disease, urinary problems and skin conditions in El Salvador and in Guatemala (Gonzalez-Ayala, 1994; MacVean, 2006). These traditional uses may be associated with the antibacterial isoflavans that occur in this species (Hori et al., 2004), or due to other constituents with different modes of action which are yet to be elucidated. Interestingly, another species from Mexico, *E. platycarpa* Pennell & Saff., is used traditionally for kidney and bladder infections and for complications of diabetes (Naváez-Mastache et al., 2006). One of the major components isolated from the branches and leaves of the latter species, 3-*O*-acetyloleanolic acid, decreased body weight and glucose level in streptozotocin-induced diabetic rats (Naváez-Mastache et al., 2006).

A decoction of the styli of *Zea mays* L. is used orally in Guatemala, Belize and El Salvador to treat kidney disease and urinary problems (Balick and Arvigo, 2015; Girón et al., 1991; Gonzalez-Ayala, 1994; Kufer et al., 2005). In Mexico this preparation is also used to manage diabetes (Andrade-Cetto et al., 2006; Andrade-Cetto and Heinrich, 2005). Accordingly, Suzuki et al. (2005) showed a positive effect of the style of this species on streptozotocin-induced diabetic nephropathy (Suzuki et al., 2005). The flavones, chrysoeriol 6-*C*-β-boivinopyranosyl-7-*O*-β glucopyranoside and chrysoeriol 6-*C*-β-L-boivinopyranoside, have been isolated from the style of this species, and they exhibited glycation inhibitory activity (Suzuki et al., 2003), which provides some scientific explanation for the traditional use for diabetes in Mexico.

In Belize a decoction of the bark of *Guazuma ulmifolia* Lam. is consumed orally to manage diabetes and treat urinary problems and it is used externally to treat skin sores and infections (Balick and Arvigo, 2015). This species is also used in Panama to treat kidney disease (Duke, 1986) and in Honduras to treat urinary problems (Lentz et al., 1998). In Mexico an infusion of the bark of *G. ulmifolia* is used to treat type-2 diabetes (Andrade-Cetto and Heinrich, 2005) and extracts of this species have been found to lower plasma glucose in animal studies (Alarcon-Aguilara et al., 1998). There are limited published data on the phytochemical constituents that might mediate the observed pharmacological effects of this species.

We found reports of the use of *Piper auritum* Kunth in Central America to manage diabetes and to treat cardiovascular disease, kidney disease and skin conditions (Balick and Arvigo, 2015; Barrett, 1994; Coe, 2008; Ferrier, 2014; House and Sanchez, 1997). A pharmacological study found that an extract of this species has antidiabetic effects (Gutierrez, 2012) and the results of an *in vitro* and *in vivo* study suggest that this species prevents oxidative stress and renal damage associated with diabetes (Perez Gutierrez et al., 2012). This species also requires further study to elucidate the biologically active constituents relevant to diabetes and the traditional uses.

Jatropha curcas L. is a large shrub widely used in traditional medicine in Central and South America, Africa, Asia and Middle East (Abdelgadir and Van Staden, 2013). We found reports of the use of this species to treat urinary problems and skin conditions in Guatemala, Belize, and El Salvador (Balick and Arvigo, 2015; Girón et al., 1991; Gonzalez-Ayala, 1994). Animal studies showed that the extract of the leaf and root of this species has hypoglycaemic activity, and it reduced cholesterol and triglyceride levels (Mishra et al., 2010; Muhammad 2013) and has wound healing properties (Esimone et al., 2008; Shetty et al., 2006; Villegas et al., 1997). Igbinosa et al. (2011) concluded the polyphenols were important for bioactivity. The anti-diabetic effects of the leaves of this species, including hypoglycaemic and antioxidant effects observed in streptozotocin-induced diabetic rats, are suggested to be associated with the flavonoids rhoifolin, isoorientin and isoquercetrin (El-Baz et al., 2014). This species is associated with anti-inflammatory, antimicrobial and antioxidant activities (Abdelgadir and Van Staden, 2013).

4 Conclusion

In this review we found that out of 105 species reported to be used to manage diabetes in Central America, only seven species are reported 3 or more times while 84 other species are reported in just one study. Similarly to what has been observed for the distribution of overall medicinal plant knowledge (Barrett, 1995), it seems that the shape of the distribution of knowledge of medicinal plants used to manage diabetes has a "long tail". Some pharmacological studies provide some scientific basis to explain the traditional uses of the species with at least 3 independent reports. Extracts from many of these species showed hypoglycaemic effects in animal models of diabetes. However, in many cases the specific mechanisms and the active compounds causing this effect are unknown and there is a lack of RCTs for most of the species.

There are many challenges associated with understanding the use of plants as medicines. Knowledge of the traditional uses, the plant parts used, the preparations and the routes of administration can be multiple and complex for one species. Furthermore, robust studies to understand any scientific basis to explain recorded traditional uses are often lacking. Although many studies describe pharmacological activities *in vitro* and/or *in vivo* that may provide some scientific basis to explain a traditional use relevant to diabetes, additional complexities such as the method(s) of preparation, the route of administration encompassing bioavailability and pharmacokinetics and dose are often not considered. Therefore for many species, more scientific research is needed to understand any pharmacological basis that might explain traditional uses, and also the sustainable and appropriate uses of plants as medicines. One of the major challenges for research on plants as medicines is the lack of available chemically-characterised and standardised preparations for investigation, particularly in RCTs, but also for many pharmacological studies. These issues were also observed for the main recorded species in this study, in relation to the scientific basis for their use in diabetes. More scientific studies are therefore needed to understand the pharmacological effects of species used traditionally for diabetes, which are directly correlated with chemically-characterised extracts. For those species where pharmacological studies are most promising to modulate parameters of diabetes, more robust clinical studies, also investigating standardised extracts, are needed to understand efficacy from both the traditional use and potential use perspectives. Indeed, even one of the most widely studied species relevant to diabetes (in previous studies and one of the most reported species in the present study), *Momordica charantia*, when evaluated in a Cochrane Review it was revealed that there were issues with the quality of clinical trial data and methods were flawed due to the variability of preparations of this plant used in the interventions; thus it was concluded that there was no significant change in reliable parameters of glycaemic control, compared to the diabetes drugs, metformin and glibenclamide (Ooi et al., 2012).

The approach used in this study was to investigate both the medicinal plants reported for the management of diabetes and its sequelae. By using this approach we provided a more complete view on the use of medicinal plant species to manage diabetes in Central America than by looking only at the species reported for the management of diabetes. Interestingly, several of the species that are used to manage diabetes in Central America are also used to treat conditions that may arise as consequence of diabetes such as kidney disease, urinary problems and skin conditions. The contemporaneous presence of many phytochemicals with potentially multiple biological activities it is often a hallmark of the practice of phytotherapy. For example, the leaves of *Neurolaena lobata* are widely used both to manage diabetes and to treat skin conditions. In the case of the use of medicinal plants to treat a metabolic disorder such as diabetes, we suggest that it is useful to use a syndromic approach that includes the multiple uses of plant species for conditions and symptoms related to diabetes, and investigate how these uses relate to their phytochemical and biological activities.

Accordingly, McCune and Johns (2002 and 2003) looked at the anti-oxidant properties of species used in the treatment of symptoms of diabetes among the peoples of the boreal forest of Eastern Canada and Leduc et al. (2006) developed a quantitative methodology to identify species with anti-diabetic properties that takes in account the use of species in the treatment of symptoms of diabetes.

The value of these medicinal plants and their associated knowledge may have relevance in the potential drug development in the future, but they are also of value for their present use among the population of Central America. Considering the huge economic cost of diabetes to both individuals and society in Central American countries (Barcelo et al., 2013), that only few countries have full coverage for diabetics in the formal healthcare system (Aschner et al., 2014), and that the risk of developing type2 diabetes is associated with a low socio-economic position (Agardh et al., 2011), it is important to highlight and understand any effective plant remedies to manage diabetes, and the associated local knowledge, to assist with providing a valuable, cost-effective, sustainable and culturally appropriate health care service to the population of Central America.

Species used to manage diabetes	**DM**	**CD**	**KD**	**SI**	**UP**	**VL**	**Total**	**Country**	**Plant part**	**Mode of use**	**Evidence**
***Momordica charantia* L.** (Cucurbitaceae)	9		1	5			15	NI, GU, BE, PA	Lf, st	Int.	DM: Animal studies showed hypoglycaemic effect (Harinantenaina et al., 2006; Reyes et al., 2006; Sathish et al., 2005; Shetty et al., 2005). SI: Several studies showed evidence that this species has broad-spectrum anti-microbial activity (Grover and Yadav, 2004; Ooi et al., 2010).

Species used to manage diabetes	DM	CD	KD	SI	UP	VL	Total	Country	Plant part	Mode of use	Evidence
***Neurolaena lobata* (L.) R.Br. ex Cass.** (Asteraceae)	6			12			18	BE, GU, NI	Lf	Int.	DM: leaf extracts decrease significantly blood glucose in mice (Aguilar Santa-Maria et al., 2009; Gupta et al., 1984) SI : antimicrobial activity (Nayak et al., 2014). Extract showed anti-ulcerogenic and anti-nociceptive effect (Gracioso et al., 2000; Gracioso et al., 1998). Anti-inflammatory activity and several sesquiterpene lactones that mediate this activity have been identified (McKinnon et al., 2014; Walshe-Roussel et al., 2013)
***Tecoma stans* (L.) Juss. ex Kunth** (Bignoniac	6						6	GU, SA	Lf, Ba, Tw	Int.	DM: extracts have hypoglycaemic properties on animal models (Román-Ramos et al., 1990)

Species used to manage diabetes	DM	CD	KD	SI	UP	VL	Total	Country	Plant part	Mode of use	Evidence
eae)											
***Persea americana* Mill.** (Lauraceae)	5		1	1	1		8	NI, GU, BE, SA	Lf, Ba, Se		DM: Hypoglycaemic properties have been shown in animal studies (Antia et al., 2005; Brai et al., 2007; Ezejiofor et al., 2013; Gondwe et al., 2008)
***Psidium guajava* L.** (Myrtaceae)	4			6			10	GU	Lf	Int.	DM: extracts have hypoglycaemic properties on animal models (Mukhtar et al., 2004; Mukhtar et al., 2006; Oh et al., 2005; Ojewole 2005; Shen et al.,2008) SI: antimicrobial and analgesic and anti-inflammatory properties (Gutiérrez et al., 2008).
Anacardium occident	3		1	5	1		10	GU, PA	Lf, Ba	Int.	DM: extracts have hypoglycaemic and anti-inflammatory effect on animal models (Esimone et al., 2001; Ojewole, 2003; Olatunji et al., 2005; Sokeng et al., 2001)

Species used to manage diabetes	DM	CD	KD	SI	UP	VL	Total	Country	Plant part	Mode of use	Evidence
***ale* L.** (Anacardiaceae)											
***Hamelia patens* Jacq.** (Rubiaceae)	3		1	5	1		10	SA, GU, BE	Lf	Int.	DM: one study suggests that the extract of this species have hypoglycaemic properties (Pandurangan et al., 2013). Extracts have anti-microbial (Camporese et al., 2003), anti-inflammatory (Sosa et al., 2002) and some wound healing activity (Gomez-Beloz et al., 2003).
Bursera simaruba (L.) Sarg. **(Burseraceae)**	2		4	5	2		13	BE	Ba	Int.	DM: Also used in Mexico to manage diabetes (Andrade-Cetto and Heinrich, 2005); Animal studies showed anti-microbial, anti-inflammatory activity of the extracts (Camporese et al., 2003; Bork et al., 1996; Sosa et al., 2002; Noguera et al., 2004)

Species used to manage diabetes	DM	CD	KD	SI	UP	VL	Total	Country	Plant part	Mode of use	Evidence
Carica papaya L. **(Caricaceae)**	2			8			10	BE, GU	Ro, Lf	Int.	DM and SI: Extracts have hypoglycaemic, hypolipidaemic and wound healing activities (Maniyar and Bhixavatimath, 2012; Adeneye et al., 2009; Juárez-Rojop et al., 2012; Sasidharan et al., 2011)
Bixa orellana L. **(Bixaceae)**	2			3	1		6	BE, GU	Ro	Int.	DM: Extracts can have both hypoglycaemic or hyperglycaemia-inducing activity depending on how the extract is prepared (Morrison et al., 1990; Quanico et al., 2008; Russell et al., 2008) and a hypolipidaemic effect (Ferreira et al., 2013).
Cecropia obtusifolia Bertol. **(Urtic**	2		1	1			4	BE, GU	Lf.	Int.	DM: Extracts have hypoglycaemic effect (Andrade-Cetto and Wiedenfeld, 2001; Herrera-Arellano et al., 2004; Pérez-Guerrero et al., 2001; Revilla-Monsalve et al., 2007; Román-Ramos et al., 1990) A clinical trial showed beneficial effects of an extract of this species administered as an adjunct on type-2 diabetes patients (Herrera-Arellano et al., 2004). Hypoglycaemic effect on type 2 diabetic patients (Revilla-Monsalve et al., 2007).

Species used to manage diabetes	DM	CD	KD	SI	UP	VL	Total	Country	Plant part	Mode of use	Evidence
aceae)											
Tridax procumbens (L.) L. **(Asteraceae)**	2		1				3	GU	Lf.	Int.	DM: extracts of the leaves and of the whole plant have antidiabetic and anti-hyperlipidemic activity (Bhagwat et al., 2008; Pareek et al., 2009; Petchi et al., 2013)
Acosmium panamense (Benth.) Yakovle	2						2	BE	Lf., Ba	Int.	DM: Animal studies of the extract showed hypoglycaemic activity (Andrade-Cetto and Wiedenfeld, 2004)

Species used to manage diabetes	DM	CD	KD	SI	UP	VL	Total	Country	Plant part	Mode of use	Evidence
v **(Fabaceae)**											
Quassia amara L. **(Simaroubaceae)**	2						2	GU, SA	Lf	Int.	DM: Animal studies showed antidiabetic activity of the extracts of this species (Ferreira et al., 2013; Husain et al., 2011)
Aristolochia grandiflora Sw. **(Aristolochiacea**	2						2	BE	-	Int.	No evidence for DM((note: no data about the content of aristolochic acids, potentially toxic)

Species used to manage diabetes	DM	CD	KD	SI	UP	VL	Total	Country	Plant part	Mode of use	Evidence
e)											
Syzygium jambos L. Alston **(Myrtaceae)**	2						2	GU, SA	Lf, Se	Int.	No evidence for DM
Combretum fruticosum (Loefl.) Stuntz **(Co**	2						2	BE, GU	Lf	Int.	No evidence for DM

Species used to manage diabetes	DM	CDD	KD	SI	UP	VL	Total	Country	Plant part	Mode of use	Evidence
mbretaceae)											
Artemisia absinthium L. **(Asteraceae)**	2						2	GU	Lf	Int	DM: Extract of this species has antihyperglycaemic activity on animals (Daradka et al., 2014). Extract has *in vitro* glucosidae and lipase inhibitory activities (Ramírez et al., 2012).
Catharanthus roseus (L.) G. Don **(Apocynace**	2						2	BE, SA	Lf, Fw	Int.	DM: Extracts have *in vivo* hypoglycaemic effect (Islam et al., 2009; Jayanthi et al., 2010; Mostofa et al., 2007; Nammi et al., 2003; Natarajan et al., 2012; Rasineni et al., 2010) and reduce serum cholesterol and triglycerides (Antia et al., 2005).

Species used to manage diabetes	DM	CD	KD	SI	UP	VL	Total	Country	Plant part	Mode of use	Evidence
ae)											
Acrocomia aculeata (Jacq.) Lodd. ex Mart. **(Arecaceae)**	2						2	BE, GU	Lf, Fr	Int.	DM: Extract has *in vivo* hypoglycaemic effect (Pérez et al., 1997; Perez et al., 1992)

Table 1. Medicinal species used to manage diabetes reported in at least 2 sources.
Species used to manage diabetes: The Plant List full accepted name and family (in bold)
Country: Ni=Nicaragua, GU=Guatemala, BE=Belize, SA=El Salvador, CR=Costa-Rica, PA=Panama.
Reports from different sources by disease category: DM= Diabetes, **CD**= Cardiovascular disease, **KD**= Kidney disease, **SI**= Skin conditions, **UP**= Urinary Problems, VL: Vision loss. **Total**= total of reports for all the disease categories considered
Plant part: Lf= leaf, St= stem, Ba= Bark, Se= Seed, Ro= root, Fw= flower, Fr= fruit. ; **Mode of use:** Int.= internal (oral), ext= external (topic)

Species used to treat skin conditions	Family	Country	Parts used	Mode of use	Sources
Neurolaena lobata (L.) R.Br. ex Cass.	Asteraceae	NI, BE, GU, PA	leaf	ext. & int.	12
Carica papaya L.	Caricaceae	BE, PA, SA, NI	latex, leaf, fruit, bark	ext.	8
Acalypha aristata Kunth	Euphorbiaceae	NI, GU, BE	leaf, whole plant, bark, sap	ext. & int.	7
Psidium guajava L.	Myrtaceae	NI, GU, BE	bark, fruit, leaf	ext. & int.	6
Cassia grandis L.f.	Fabaceae	BE, NI	fruit, leaf, stem, root	ext. & int.	6
Bursera simaruba (L.) Sarg.	Burseraceae	GU, NI, BE	bark, leaf	ext. & int.	5
Momordica charantia L.	Cucurbitaceae	NI, GU, BE	leaf , stem	ext. & int.	5
Anacardium occidentale L.	Anacardiaceae	NI	bark, leaf	ext. & int.	5
Hamelia patens Jacq.	Rubiaceae	BE, NI, SA	leaf, whole plant, flower	ext. & int.	5
Passiflora quadrangularis L.	Passifloraeae	NI, PA	leaf, stem	ext. & int.	5
Senna alata (L.) Roxb.	Fabaceae	NI	leaf, fruit, flower	ext. & int.	5
Bryophyllum pinnatum (Lam.) Oken	Crassulaceae	NI, GU, BE	leaf	ext.	5
Commelina erecta L.	Commelinaceae	BE, NI	leaf and stem	ext. & int.	5
Cordia alliodora (Ruiz & Pav.) Oken	Boraginaceae	BE, NI	Seed, leaf	ext. & int.	5
Heliotropium indicum L.	Boraginaceae	BE, NI	leaf, whole plant	ext. & int.	5

Species used to treat skin conditions	Family	Country	Parts used	Mode of use	Sources
Mangifera indica L.	Anacardiaceae	NI	bark, fruit, leaf	ext. & int.	5
Rhizophora mangle L.	Rhizophoraceae	BE, NI	bark	ext. & int.	5
Spondias mombin L.	Anacardiaceae	BE, NI	bark, leaf	ext. & int.	5
Spondias purpurea L.	Anacardiaceae	NI, BE, SA	bark, leaf	ext. & int.	5
Desmodium adscendens (Sw.) DC.	Fabaceae	NI	leaf, whole plant, root	int.	4
Hyptis verticillata Jacq.	Lamiaceae	NI	leaf, whole plant, root	ext. & int.	4
Lygodium venustum Sw.	Lygodiaceae	BE, NI	leaf	ext.	4
Dysphania ambrosioides (L.) Mosyakin & Clemants	Amaranthaceae	GU, NI, BE	whole plant, leaf	ext.	4
Lantana camara L.	Verbenaceae	BE, PA,GU, NI	leaf	ext.	4
Xiphidium caeruleum Aubl.	Haemodoraceae	BE, NI, PA	leaf	ext. & int.	4
Capsicum annuum var. *glabriusculum* (Dunal) Heiser & Pickersgill	Solanaceae	NI	seed, fruit, leaf, flower	ext. & int.	4
Capsicum chinense Jacq.	Solanaceae	NI	seed, fruit, leaf, flower	ext. & int.	4
Coccoloba uvifera (L.) L.	Polygonaceae	NI	bark, leaf	int.	4
Gynerium sagittatum (Aubl.) P.Beauv.	Poaceae	NI	root	int.	4
Manilkara zapota (L.) P.Royen	Sapotaceae	NI	stem, sap	ext.	4
Oryza sativa L.	Poaceae	NI	seed, stem	ext. & int.	4
Pentaclethra macroloba (Willd.) Kuntze	Fabaceae	NI	bark	ext. & int.	4

Species used to treat skin conditions	Family	Country	Parts used	Mode of use	Sources
Piper peltatum L.	Piperaceae	NI, GU, BE, HO	leaf	Ext.	4
Senna reticulata (Willd.) H.S.Irwin & Barneby	Fabaceae	Ni	leaf, root	int.	4
Simarouba amara Aubl.	Simaroubaceae	BE, NI, GU	leaf, fruit, bark, seed	ext. & int.	4
Solanum lycopersicum L.	Solanaceae	NI	leaf	ext.	4
Struthanthus cassythoides Millsp. ex Standl.	Loranthaceae	BE, NI	leaf, whole plant	ext. & int.	4
Theobroma cacao L.	Sterculiaceae	NI	seed, leaf	ext.	4
Cecropia peltata L.	Urticaceae	NI, BE, HO	leaf	ext. & int.	3
Pachira aquatica Aubl.	Bombacaceae	Ni	bark	int.	3
Piper auritum Kunth	Piperaceae	NI, Ho, BE	leaf	ext. & int.	3
Coix lacryma-jobi L.	Poaceae	NI	seed, root	int.	3
Bixa orellana L.	Bixaceae	NI, BE, HO	leef, seed	ext. & int.	3
Jatropha gossypiifolia L.	Euphorbiaceae	NI	leaf	int.	3
Psychotria poeppigiana Müll.Arg.	Rubiaceae	NI	fruit, leaf, stem, root	ext. & int.	3
Byrsonima crassifolia (L.) Kunth	Malpighiaceae	BE, GU, NI	bark, leaf	ext. & int.	3
Cuscuta americana L.	Convolvulaceae	NI	leaf, stem	ext.	3
Dalbergia brownei (Jacq.) Urb.	Fabaceae	NI	bark, leaf, stem	ext. & int.	3
Desmodium barbatum (L.) Benth.	Fabaceae	NI	leaf, root	int.	3
Gliricidia sepium (Jacq.) Walp.	Fabaceae	BE, NI	bark, leaf	ext. & int.	3
Hamelia rovirosae Wernham	Rubiaceae	BE, NI	fruit, leaf, stem,	ext. & int.	3

Species used to treat skin conditions	Family	Country	Parts used	Mode of use	Sources
			root		
Hiraea quapara (Aubl.) Sprague	Malpighiaceae	NI	leaf	ext	3
Ipomoea mauritiana Jacq.	Convolvulaceae	NI	leaf	ext. & int.	3
Ipomoea pes-caprae (L.) R. Br.	Convolvulaceae	NI	leaf	ext. & int.	3
Jatropha curcas L.	Euphorbiaceae	BE, GU, SA	leaf, latex	ext.	3
Mucuna sloanei Fawc. & Rendle	Fabaceae	NI	sap	ext.	3
Olyra latifolia L.	Poaceae	NI	leaf, root	ext. & int.	3
Pouteria sapota (Jacq.) H.E.Moore & Stearn	Sapotaceae	NI	bark, leaf, seed	ext. & int.	3
Saccharum officinarum L.	Poaceae	NI	leaf, stem	ext. & int.	3
Smilax spinosa Mill.	Smilacaceae	NI, GU, BE, HO	root	ext. & int.	3
Solanum torvum Sw.	Solanaceae	BE, NI	leaf, root	ext.	3
Spermacoce laevis Lam.	Rubiaceae	PA, NI	leaf, whole plant	ext.	3

Table 2 Plants used to treat skin conditions
Species used to treat skin conditions: The Plant List full accepted name **; Country:** Ni= Nicaragua, GU= Guatemala, BE= Belize, SA= El Salvador, CR=Costa-Rica, PA= Panama. **; Mode of use:** int.= internal (oral), ext= external (topic) **; Sources**: number of sources where the species was reported for the treatment of skin conditions

Species used to treat kidneys disease	Family	Country	Parts used	Mode of use	Sources
Bursera simaruba (L.) Sarg.	Burseraceae	BE, GU, PA	leaf, bark, fruits	int.	4
Equisetum myriochaetum Schltdl. & Cham.	Equisetaceae	GU, SA	Aerial part, whole	int.	3
Hymenaea	Fabaceae	GU, SA,	Bark, leaf	int.	3

courbaril L.		NI			
Sambucus canadensis L.	Adoxaceae	GU, SA	Flower, bark, leaf	int.	3
Aloe vera (L.) Burm.f.	Liliaceae	SA, BE	leaf, gel	int.	2
Cecropia peltata L.	Urticaceae	SA, BE	leaf, bark	int.	2
Cocos nucifera L.	Arecaceae	SA, BE	water from fruit	int.	2
Eysenhardtia adenostylis Baill.	Fabaceae	SA, GU	stem, bark	int.	2
Pachira aquatica Aubl.	Bombaceae	BE	seed, fruit	int.	2
Zea mays L.	Poaceae	BE, SA	styli	int.	2

Table 3 Plants used to treat kidneys disease
Species used to treat kidney disease: The Plant List accepted full name**; Country:** Ni= Nicaragua, GU= Guatemala, BE= Belize, SA= El Salvador, CR=Costa-Rica, PA= Panama. **; Mode:** int= internal (oral), ext=external (topic)**; Sources**: number of sources where the species was reported for the treatment of kidney disease

Species used to treat urinary problems	**Family**	**Country**	**Parts used**	**Mode of use**	**Sources**
Zea mays L.	Poaceae	BE, SA, GU	styli	Int.	5
Arthrostemma ciliatum Pav. ex D. Don	Melastomataceae	PA, BE, HO, CR	stem, whole plant	int.	4
Cocos nucifera L.	Arecaceae	BE, SA, GU	water from fruit	int.	3
Acalypha aristata Kunth	Euphorbiaceae	GU, BE	whole	int.	2
Bursera simaruba (L.) Sarg.	Burseraceae	PA, GU	bark, fruits	int.	2
Jatropha curcas L.	Euphorbiaceae	BE, SA	leaf, bark	int.	2
Equisetum myriochaetum Schltdl. & Cham.	Equisetaceae	SA, GU	whole	int.	2
Guazuma ulmifolia Lam.	Malvaceae	BE, HO	bark	int.	2
Euphorbia hirta L.	Euphorbiaceae	BE, GU	leaf, bark	int.	2

Capraria biflora L.	Scrophulariaceae	BE, GU	leaf, bark	int.	2
Passiflora coriacea Juss.	Passifloraceae	SA, GU	leaf	int.	2

Table 4 Plants used to treat urinary problems
Species used to treat urinary problems: The Plant List full accepted name **; Country:** Ni= Nicaragua, GU= Guatemala, BE= Belize, SA= El Salvador, CR=Costa-Rica, PA= Panama. **; Mode of use:** int=internal (oral), ext=external (topic) **; Sources**: number of sources where the species was reported for the treatment of urinary problems

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The use of plants in the traditional management of diabetes and its sequelae in Central America

Reviewed primary data

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Entered data in a database: reports of 535 species, including 104 species used to manage diabetes

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Reviewed evidence for most reported species

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Found high variation in the availability and quality of pharmacological, chemical and clinical studies