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Medicinal plants with antidiabetic activity used in the traditional medicine in Bolivia: A review

BACHELOR'S THESIS

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Declaration

I hereby declare that I have done this thesis entitled Medicinal plants with antidiabetic activity used in the traditional medicine in Bolivia: A review independently, all texts in this thesis are original, and all the sources have been quoted and acknowledged by means of complete references and according to Citation rules of the FTA.

In Prague 14.4.2022

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Peková Lucie

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Abstract

The present study aimed to document the traditional use of medicinal plants used to treat diabetes mellitus Type II in Bolivia. Based on 17 scientific sources devoted to ethnobotany, were identified 35 medicinal plant species distributed in 21 botanical families, of which 55 % (18 species) are native to Bolivia and 45 % (15 species) are introduced. The botanical families with the highest representation of species were *Asteraceae* (7 species, 19 %) and *Fabaceae* (6 species, 17 %). The most frequented growth forms were herbs (14 species, 34 %) and trees (12 species, 29 %). Leaves (13 reports, 30 %) were the most frequently used plant parts, followed by roots (6 reports, 14 %), and bark (4 reports, 9 %), mostly prepared as an infusion (16 reports, 40 %) and decoction (13 reports, 33 %). From the available scientific studies, 25 medicinal species were verified for their antidiabetic properties with positive results, for the remaining 10 species, no study was found to evaluate their antidiabetic effects. It is therefore necessary provide more biochemical and clinical analysis of medicinal plants to make better use of their potential.

Key words: Diabetes, ethnobotany, herbal medicine, pharmacological evaluation, traditional medicine

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1. Introduction

Diabetes mellitus (DM) is a group of metabolic diseases that are described as the result of impaired insulin secretion, insulin action, or a combination of both. Most of the food a person ingests is broken down by the body into simple sugars - glucose, which the body uses as a source of energy. The hormone insulin is needed to use this sugar. The cells of a person who has diabetes are therefore unable to use this sugar. This leads to a rise in blood sugar levels and hyperglycaemia occurs, which is the main symptom of the disease diabetes mellitus (American Diabetes Association 2007).

This illness is a critical global issue, affecting around 422 million people globally, the majority of whom live in low- and middle-income countries. Each year, diabetes claims the lives of around 1.5 million individuals, with the incidence of the disease gradually increasing in recent decades (WHO 2019).

It was predicted in 2007 that there will be 366 million patients globally by 2030 (Lago et al. 2007), but as World Health Organization (WHO) statistics from 2019 show, the numbers have risen rapidly and are still rising (WHO 2019). Another estimate for the year 2040 is over 640 million patients, indicating a serious problem that will cost not only many lives but a burden on health facilities and the associated financial costs (Marín-Peñalver et al. 2016).

Traditional medicine (TM) is important worldwide, indispensable and one of the main sources of medical care, or it serves as a supplement to conventional treatment. For millions of people in rural areas, native healers are their main and often the only providers of health care (WHO 2013).

The health of the Bolivian population has not been a priority for the government for a long time. The current health reform only began to take shape in 2011 with the presentation of a preliminary draft law on the unified health system, which focused on primary care, social medicine and the intercultural community health model. However, despite all the efforts and the adoption of the law in 2013, the current health conditions have not improved much and low-income populations, which are mainly indigenous people in rural areas, are still struggling to treat their illnesses (Hita 2014). However, in this new health legislation, the practice of traditional Bolivian medicine, defined by Law 459, has been incorporated into the national health system (Ministry of Health 2013).

Traditional medicine is globally important not only for Bolivia. According to WHO, it is one of the main sources of health care or serves as a complement to it. It is particularly important in rural areas, where traditional healers are often the only or main source of medical care. Traditional medicine's main strengths include its affordability and infrastructure for low-income populations, and it is consistent with the traditional values and beliefs of indigenous populations (WHO 2019).

Although medicinal plants have a long history of usage in the treatment of disease, contemporary medicine takes time to embrace and apply them. Alternative medicine, on the other hand, continues to attract many people. A rise in the number of patients adopting natural ingredients to regulate their condition has come from a large amount of pharmacological research into the antidiabetic benefits of medicinal plants.

Traditional herbal treatments were utilized to treat diabetes and its consequences before the discovery of insulin and other blood glucose-lowering medications. Currently, more than 800 species of medicinal plants with potential antidiabetic effects are used worldwide to treat diabetes (Arumugam et al. 2013). Traditional medicinal plants offer anti-diabetic properties that are reported to have almost no negative side effects. They are high in anti-diabetic chemicals such flavonoids, alkaloids, phenolics, and tannins, which increase pancreatic tissue efficiency by boosting insulin production or lowering glucose absorption in the intestine (Bindu & Narendhirakannan 2019).

There are many indigenous groups and communities in Bolivia, each of which has its own relationship to the environment and the use of local medicinal plants. Medicinal plants are a key approach to health care not only in rural areas but also in large cities (Macía et al. 2005). The Kallaways, Jampiris (Andean highlands and valleys), Ipayes, and Chiman (tropical lowlands) are indigenous communities that most regularly practice and propagate traditional medicine (Kokoska & Cusimamani 2008).

Bolivians prefer traditional medicine mainly because of the lack of access to large hospitals, because of affordability, because of the lack of trust in the city doctor and also because of traditional values and beliefs (Perry & Gesler 2000; Quiroga et al. 2012).

Approximately 80 % of Bolivians (over 6 million people) have used traditional medicine healers at some point in their lives. Traditional medicine has a stronghold in Bolivia due to widespread scepticism of modern treatment, which is fueled by financial, infrastructure, psychological, and cultural barriers (Kokoska & Cusimamani 2008).

Medicinal herbs are being utilized in Bolivian towns such as Chocabamba, La Paz, Potosi, and Sucre, as well as in the countryside. This is because many of these people originate from peasant villages and keep some of their traditions. There are kiosks or small marketplaces dedicated to medicinal plants in major cities (Macía et al. 2005).

According to WHO data, diabetes mellitus affects 6.6 % of Bolivia's population, and the disease is responsible for 4 % of all deaths in the country (WHO 2016; WHO 2019). The disease affects women more (7.7 %) than men (5.5 %) and overweight (50 %) and obesity (16 %) are considered the most risky factors (WHO 2016). The city with the greatest diabetes prevalence in Bolivia is Santa Cruz (8.6 %), while El Alto has the lowest incidence (2 %) (Vargas 2011). As Bolivia is a low- and middle-income country, the growing prevalence of diabetes is expected to place an excessive burden on the local health system as well as increasing mortality (Kruk et al. 2015; Leyns et al. 2021).

In addition to the risk of overloading the local health system, diabetes also significantly affects the country's budget. A 2003 study found that the direct and indirect costs of diabetes were $ 2,2800,000, which is 1047 % of the excessive costs of treating diabetes (Barceló et al. 2003).

The female population, as well as population over the age of 30, are more likely to develop diabetes, due to a lack of knowledge and awareness of the elements that lead to the illness, as well as a lack of information regarding prevention. Only around half of people in Bolivia diagnosed with diabetes are aware of their condition, and only about 33 % of them are prepared to take preventative steps (Vargas 2011).

Since diabetes mellitus is a silent disease in its first stages, without symptoms, which can have binding consequences, these consequences can be prevented by early diagnosis and regular screening. Also, greater awareness of the Bolivian population and efforts to involve indigenous cultures in primary medical care could lead to an improvement in the current, almost epidemiological, status of diabetes in Bolivia.

This bachelor thesis is prepared as an annotated article entitled Medicinal plants with antidiabetic activity used in the traditional medicine in Bolivia: A review. Manuscript has been accepted in the journal Boletin Latinoamericano y del Caribe de Plantas Medicinales y Aromáticas and is in press (Appendix 1).

2. Manuscript – Medicinal plants with antidiabetic activity used in the traditional medicine in Bolivia: A review

Pekova L, Žiarovska J, EF Cusimamani. 2022. Medicinal plants with antidiabetic activity in the traditional medicine in Bolivia: A review. Boletin Latinoamericano y del Caribe de Plantas Medicinales y Aromáticas [in press].

Medicinal plants with antidiabetic activity used in the traditional medicine in Bolivia: A review

[Plantas medicinales con actividad antidiabética utilizadas en la medicina tradicional de Bolivia: una compilación]

2.1. Abstract

The present study aimed to document the traditional use of medicinal plants used to treat diabetes mellitus Type II in Bolivia. Based on 17 scientific sources devoted to ethnobotany, were identified 35 medicinal plant species distributed in 21 botanical families, of which 55 % (18 species) are native to Bolivia and 45 % (15 species) are introduced. The botanical families with the highest representation of species were *Asteraceae* (7 species, 19 %) and *Fabaceae* (6 species, 17 %). The most frequented growth forms were herbs (14 species, 34 %) and trees (12 species, 29 %). Leaves (13 reports, 30 %) were the most frequently used plant parts, followed by roots (6 reports, 14 %), and bark (4 reports, 9 %), mostly prepared as an infusion (16 reports, 40 %) and decoction (13 reports, 33 %). From the available scientific studies, 25 medicinal species were verified for their antidiabetic properties with positive results, for the remaining 10 species, no study was found to evaluate their antidiabetic effects. It is therefore necessary provide more biochemical and clinical analysis of medicinal plants to make better use of their potential.

Keywords: Diabetes, ethnobotany, herbal medicine, pharmacological evaluation, traditional medicine

Resumen

El objetivo del presente estudio fue documentar el uso tradicional de plantas medicinales para el tratamiento de la diabetes mellitus tipo II en Bolivia. Con base en 17 fuentes científicas sobre etnobotánica, se identificaron 35 especies medicinales distribuidas en 21 familias botánicas, de las cuales el 55 % (18 especies) son nativas de Bolivia y el 45 % (15 especies) son introducidas. Las familias botánicas con mayor representación de especies fueron *Asteraceae* (7 especies, 19 %) y *Fabaceae* (6, especies, 17 %). Las formas de crecimiento más frecuentes fueron hierbas (14 especies, 34 %) y árboles (12 especies, 29 %). Las hojas (13 informes, 30 %) fueron la parte de la planta más utilizada, seguidas de las raíces (6 informes, 14 %) y la corteza (4 informes, 9 %), preparadas especialmente como infusión (16 informes, 40 %) y decocción (13 informes, 33 %). Así mismo, con base en estudios científicos disponibles, se confirmó la actividad antidiabética de 25 especies medicinales, pero para 10 especies no se encontró ningún estudio que evalúe su efecto antidiabético. Por lo tanto, es necesario aportar más análisis bioquímicos y clínicos de las plantas medicinales para aprovechar mejor su potencial.

Palabras clave: Diabetes, etnobotánica, fitoterapia, evaluación farmacológica, medicina tradicional

2.2. Introduction

Diabetes mellitus is one of the leading causes of death in the world. Approximately 422 million people worldwide have diabetes, especially in low- and middle-income countries (WHO, 2019). Study carried out in 2007 predicted the incidence of the disease at 366 million in 2030 (Lago *et al.*, 2007), but as early as 2019, the number was much higher. Diabetes mellitus is also associated with high costs, especially due to the development of new drugs (Rowley *et al.*, 2017).

Between 65-80% of the world's population in developing countries, due to poverty and lack of access to modern medicine, depends on traditional medicine. Medicinal plants are generally easily accessible, cheap, and have very low side effects. Different parts of plants are used such as leaves, flowers, fruits, seeds, roots, bulbs, etc.; and plants that grow in the wild or are cultivated are used (Cussy-Poma *et al.*, 2017; Fernández *et al.*, 2019).

Every day more attention is paid to the use of medicinal plants to treat chronic diseases, including diabetes. Phytotherapy has an irreplaceable role in the treatment of diabetes, mainly due to its adjuvant effect, which can lead to a reduction in the consumption of conventional pharmaceutical products and delay the onset of late diabetes complications (Koupý and Rudá-Kucerová, 2015; Gallego Muñoz and Ferreira Alfaya, 2015).The hypoglycemic activity of the phytopreparations is due to their ability to restore the functions of pancreatic β cells, stimulate insulin release, reduce absorption glucose in the intestine or influencing metabolic-dependent processes of insulin (Sychrová, 2017).

In Latin America, many people with diabetes have limited access to health care, and according to a study by Barceló *et al.* (2003), the cost of diabetes mellitus (DM) was estimated between US$ 102 and US$ 123 billion, representing challenges to be solved by health systems and society in Latin America. The use of traditional medicine has been reported as an alternative to the high cost of conventional medicine. About 800 species of plants with antidiabetic properties have been reported based on ethnobotanical studies of medicinal plants worldwide (Mamun-or-Rashid *et al.*, 2020) and the scientific studies have confirmed the antidiabetic effects of most of them (Patel *et al.*, 2012; Zehad *et al.*, 2017). The antidiabetic activity of medicinal species is generally proven in a model of diabetes-induced by alloxan and streptozotocin in rats (Kameswararao *et al.*, 2003; Bequer Mendoza *et al.*, 2014).

According to WHO data 6.6 % of the Bolivian population have a prevalence of diabetes (WHO, 2019). The prevalence of diabetes is on the rise, especially in urban areas of Bolivia (Leyns *et al.,*2021). In the countryside, treatment is supported or diabetes is treated directly with medicinal plants. The antidiabetic effect has been scientifically confirmed in species traditionally grown in Bolivia such as *Chenopodium quinoa, Amaranthus caudatus, Chenopodium pallidicaule, Lupinus mutabilis and Smallanthus sonchifolius* (Zambrana *et al.,* 2020). There are patients with type II diabetes in Bolivia making use of medicinal plants as a primary source to treat their disease or in a complementary way to their treatment with medications recommended by conventional medicine (Quiroga and Meneses, 2012; WHO, 2019). Diabetes accounts about 4 % of all mortality in Bolivia (WHO, 2016).

There are few ethnobotanical studies on this topic but there is currently no list of plants or scientific studies that summarize the use of medicinal plants in the treatment of diabetes in Bolivia and their pharmacological evaluation. Therefore, the aim of this review is to document the traditional use of medicinal plants used to treat diabetes mellitus Type II summarizing knowledge about the management of medicinal plants with antidiabetic activity, within the framework of traditional medicine, practiced in Bolivia.

2.3. Methods

Data collection

The data were compiled from available online scientific publications which have been published in the last 20 years in order to obtain the most up-to-date data in English, Spanish. The main list was generated from a total of 17 scientific articles and books devoted to the ethnobotany of medicinal plants in the treatment of diabetes in Bolivia. Databases ScienceDirect, Researchgate, SciELO, Google Scholar, Web of Science, Scopus, were used as resources to collect data. These online databases were searched based on keywords like, the traditional use of plants to treat diabetes, medicinal uses of plants to treat diabetes, indigenous use of plants to treat diabetes, ethnobotanical surveys and ethnopharmacological studies of Bolivia. For all plants at the species level, the taxonomy according to a working list The plant list (The Plant List, 2010) and their habit and origin according to Plants of the World Online (POWO, 2019) were unified.

2.4. Results and discussion

Medicinal plants with antidiabetic potential used in traditional medicine of Bolivia

A main list was generated enlisting all the medicinal plants used in Bolivia for the treatment of type II diabetes (Table 1) with the following data: Botanical family, Scientific name, Local name, Plant part(s), Preparations, Habit, Phytogeographic Origin, and References. All the data has been summarized in one table and four figures.

Based on the obtained data were identified a total of 35 medicinal plants used for the treatment of diabetes mellitus in Bolivia, of these, 33 plants were identified at the species level and 2 plants at genus level, totally distributed in 21 families (Table 1). The botanical families with the highest representation of species (Figure 1) were *Asteraceae* (7 species, 19 %) and *Fabaceae* (6 species, 17 %), followed by three other families containing 2 species each and 16 families containing only 1 species each. A total of 18 founded plants (55 %) were native to Bolivia and 15 plants (45 %) were introduced. *Asteraceae* is one of the most widely used families in ethnomedicine in the world and South America has the highest number of *Asteraceae* species of followed by Asia (Panero and Crozier, 2016). Many species along with the secondary metabolites (volatile oils and terpenoids among others), are mainly responsible for the relevance of this family in traditional medicine. Also other ethnobotanical studies focused on treatment of diabetes mellitus with medicinal plants from around the world shows that *Asteraceae* is the most frequent botanical family (Semenya *et al.*, 2012; Kpodar *et al.*, 2015; Katiri *et al.*, 2017).

The most dominant growt form (Figure 2) were herbs (14 reports, 34 %), followed by trees (12 reports, 29 %), shrubs (12 reports, 29 %) and climbing plants (3 reports, 7%), which agrees with another ethnobotanical study focused on treatment diabetes mellitus in which herb were the most dominant growth form (Katiri *et al.*, 2017).

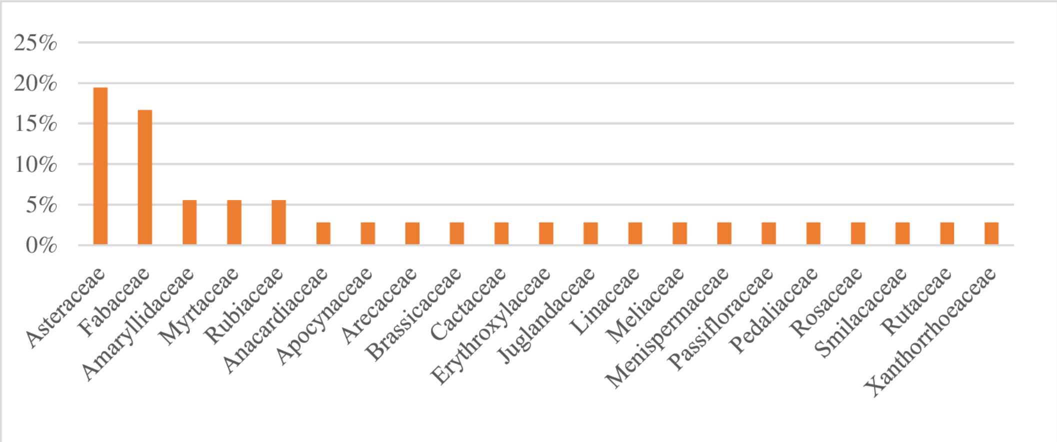

Figure 1 The most frequented botanical family of medicinal plants

The most used parts of plants are leaves (13 reports, 30%), followed by roots (6 reports, 14%), bark (4 reports, 9%) and aerial parts (4 reports, 9%) (Figure 3). The predominance of using leaves agrees with other ethnobotanical studies of treatment D. mellitus (Kadir *et al.*, 2012; Katiri *et al.*, 2017; Kargioglu and Ari, 2017; Skalli *et al.*, 2019). The preference of the leaves over the other parts of the plant is due to the leaves being the photosynthetic organs that contain the photosynthates that could be responsible for their medicinal values (Bar and Ori, 2014).

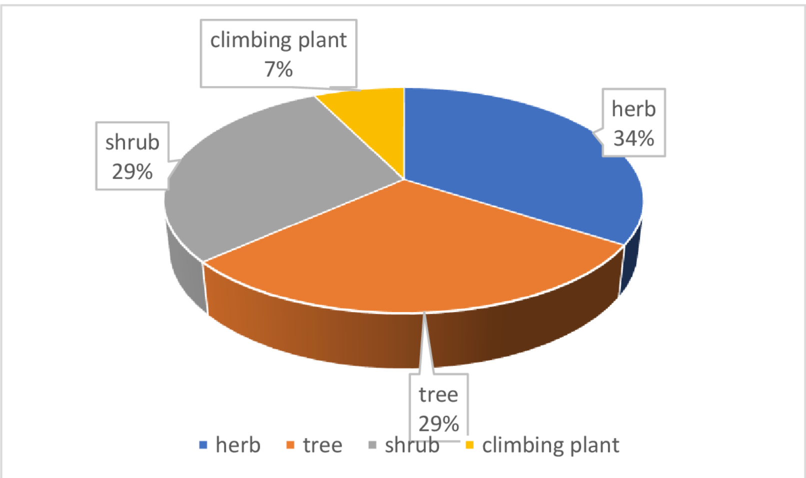

Figure 2 Habit of medicinal plants

The analysis of herbal recipes revealed that infusion (16 reports, 40 %), and decoction (13 reports, 33 %) are the most frequent preparation methods used, followed by juice (4 reports, 10 %), eating (3 reports, 8 %) and powder (2 reports, 5 %). All preparation methods are shown in Figure 4.

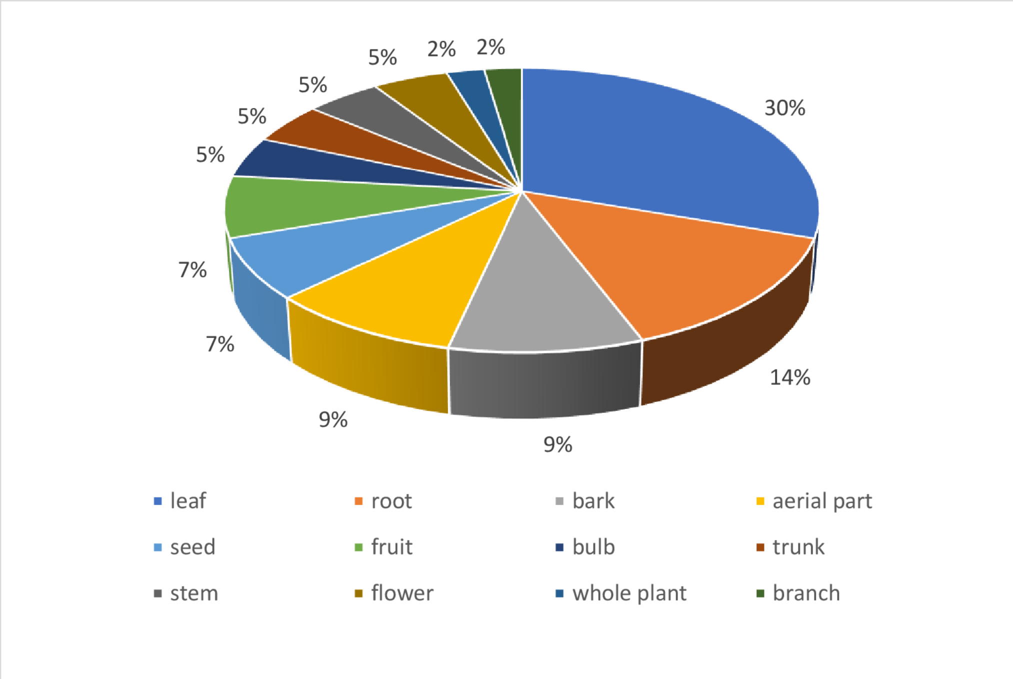

Figure 3 Plant part used

Also other ethnobotanical studies shows that infusion or decoction is the most common way of preparation herbal medicine (Kadir *et al.*, 2012; Kargioglu and Ari, 2017; Skalli *et al.*, 2019).

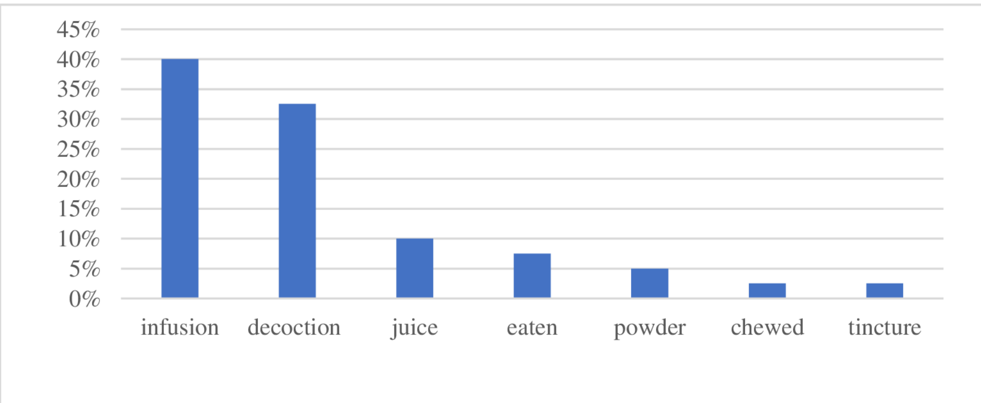

Figure 4 Methods of preparation

Table 1 Medicinal plants for the treatment of diabetes in traditional medicine in Bolivia

Scientific name	Local name	Plant part	Preparations	Habit	Origin	References
			Amaryllidaceae			
Allium cepa L.	Ajo macho	bulb	infusion, decoction	herb	I	7; 13
Allium sativum L.	Ajo	bulb	eaten raw	herb	I	15
			Anacardiaceae			
Anacardium occidentale L.	Cayo, Cayú	bark	decoction	tree	N	1; 14
			Apocynaceae			
Aspidosperma rigidum Rusby	Gabetillo	trunk	decoction	tree	N	3
			Arecaceae			
Euterpe precatoria Mart.	Ehuid'a	root	decoction	tree	N	9
			Asteraceae			
Artemisia absinthium L.	Ajenko	aerial part	infusion	herb	I	13
Baccharis genistelloides (Lam.) Pers	Carqueja; Charara; Kimsa kkuchu	aerial part, leaves	infusion	herb/shrub	N	7;8;15
Cynara cardunculus L.	Alcachofa	aerial part	decoction	herb	I	13
		leaves	infusion	herb	I	15
Smallanthus sonchifolius (Poepp.) H.Rob. Griseb	Yacón	leaves, roots	infusion, juice	herb	N	11
Schkuhria octoaristata DC.	Kanchalawa	roots	decoction	herb	N	15
Schkuhria pinnata (Lam.) Kuntze ex Thell.	Jayaq pichana	whole plant	decoction	herb	N	2
Stevia rebaudiana (Bertoni) Bertoni	Estevia	leaves	infusion	herb	I	11; 16
			Brassicaceae			
Nasturtium officinale W.T.Aiton	Berros, Ukururu, Willkayuyu	aerial part	eaten raw	herb	I	6
		Cactaceae				
Opuntia ficus-indica (L.) Mill	Penca	stem, root, flower	decoction, juice, powder	shrub	I	13

Table 1 – Medicinal plants for the treatment of diabetes in traditional medicine in Bolivia (*Continued*)

			Erythroxylaceae			
Erythroxylum coca Lam.	Coca	leaves	chewed	shrub	N	11
			Fabaceae			
Acacia sp.	Sipamë; Tipa	bark	powder	tree/shrub		1
Bauhinia guianensis Aubl.	Nishi isanuma, Nishi para; Bejuco blana	leaves	infusion	climbing plant	N	1; 14
Bauhinia rufa (Bong.) Steud.	Patevaca, Patebuey	leaves	infusion	shrub/tree	N	3
Bauhinia sp.	Camanó pahoqui	trunk	decoction	herb		1
Otholobium pubescens (Poir.) J.W.Grimes	Wallak'aya	leaves	infusion	shrub	N	13
Prosopis ruscifolia Griseb.	Aatek	leaves	infusion	tree	N	10
			Juglandaceae			
Juglans boliviana Dode	Nogal	leaves	infusion	tree	N	7;13
			Linaceae			
Linum usitatissimum L.	Linaza	seed	infusion	herb	I	15
			Meliaceae			
Swietenia macrophylla King	Mara	seed	infusion	tree	N	3
			Menispermaceae			
Abuta grandifolia (Mart.) Sandwith	Abuta	bark, branches, Root	decoction	shrub	N	11
			Myrtaceae			
Eucalyptus globulus Labill.	Eucalipto	leaves	tincture	shrub/tree	I	15
Psidium guajava L.	Guayaba	young leaves	infusion	small tree	N	3
			Passifloraceae			
Passiflora mollissima (Kunth) L.H. Bailey	Tumbo	flower	infusion	climbing plant	N	7; 13
			Pedaliaceae			
Sesamum indicum L.	Ajonjolí/Sésamo	seed	eaten	herb	I	11

Table 1 – Medicinal plants for the treatment of diabetes in traditional medicine in Bolivia (*Continued*)

Rosaceae						
Rubus fruticosus L.	Mora/Blackberry	fruit	juice	shrub	I	11
Rubiaceae						
Coffea arabica L.	Sultana	fruits	decoction	shrub/small tree	I	7
Uncaria guianensis (Aubl.) J.F. Gmel.	Uña de gato	stems, bark	decoction	climbing plant	N	12
Rutaceae						
Citrus medica L.	Cidra	fruit	juice	shrub/small tree	I	8
Smilacaceae						
Smilax aspera L.	Zarzaparrilla, Wila layu	root	decoction	shrub	I	13;17
Xanthorrhoeaceae						
Aloe vera (L.) Burm.f.	Sábila	leaves	Infusion	herb	I	13

Origin: (N) native, (I) introduced

References:

(1) (Fernández *et al.*, 2003) ; (2) (Atahuachi and Saravia, 2002); (3) (Hajdu and Hohmann, 2012); (4) (Quiroga *et al.*, 2012); (5) (Quiroga and Meneses, 2012); (6) (Paniagua Zambrana *et al.*, 2017); (7) (Macía *et al.*, 2005); (8) (Justo-Chipana and Moraes, 2015); (9) (Bourdy *et al.*, 2000); (10) (Quiroga, 2017); (11) (Ceuterick *et al.*, 2011); (12) (Gupta, 2006); (13) (Bussmann *et al.*, 2016a); (14) (Paniagua Zambrana and Bussmann, 2017); (15) (De Lucca and Zalles, 2006); (16) (Cornejo and Blacutt, 2009); (17) (Bhatta *et al.*, 2021)

Literature findings of clinical trials and pharmacological evaluation related to the use of species in the treatment of diabetes mellitus type II in Bolivia.

A total of 25 species have their antidiabetic properties verified on the basis of available scientific studies. All of these species have had their antidiabetic effect confirmed, so traditional healers in Bolivia use the medicinal plants correctly. But the antidiabetic activity was mostly proven in a model of diabetes-induced by streptozotocin and alloxan in rats. Only three clinical studies have been performed in people with *Erythroxylum coca*, *Opuntia ficus-indica* and *Linum usitatissimum*. No studies investigating or confirming the pharmacological effect of *Aspidosperma rigidum, Euterpe precatoria, Schkuhria octoaristata, Bauhinia guianensis, Bauhinia rufa, Juglans boliviana, Uncaria guianensis, Smilax aspera* have been found.

1. ***Allium cepa* L.**

A study in male Wistar rats showed that *Allium cepa* has hypoglycemic and hypolipidemic effects, and is associated with free radical scavenging properties (Campos *et al.*, 2003). The antidiabetic activity is also indicated by a study in which alloxan-induced diabetic rats were administered sulphur-containing S-methyl amino acid cysteine sulfoxide (200 mg/kg for 45 days). These rats significantly controlled both glucose and lipid levels in blood and tissue, and liver hexokinase, glucose-6-phosphatase, and HMG Co A reductase activity were also normalized (Kavishankar *et al.*, 2011).

The effects of *A. cepa* were also studied in 84 patients with diabetes mellitus type 1 and type 2 with a mean age of 44±3.87 years. Intake of 100 g of raw red onion improved oral glucose tolerance and fasting blood sugar after 4 hours. The active ingredients of *A. cepa* are considered by the study to be prophylactic and therapeutic agents in the treatment of diabetes. It manifests its antidiabetic properties through various mechanisms, the most important of which are antioxidant effects, inhibitory effects on α-glucosidase and α-amylase, reduction of insulin resistance and absorption of glucose from the intestine and increased insulin secretion (Galavi *et al.*, 2021).

2. *Allium sativum* L.

Garlic (*Allium sativum*) antidiabetic activities were demonstrated in a study in streptozotocin-induced diabetic rats given oral garlic extract (0.1; 0.25; 0.5 g/kg for 14 days). Administration of garlic extract was found to significantly reduce serum glucose, total cholesterol, triglycerides, urea, uric acid and creatinine. A comparison was also made between the effect of garlic extract and the known antidiabetic drug glibenclamide, where *A. sativum* extract was more effective (Eidi *et al.*, 2006).

Demonstrable antidiabetic activity is also confirmed by study on STZ-induced rats. Raw garlic extract was administered intraperitoneally at a dose of 500 mg/kg for seven weeks. There was a significant reduction in blood glucose (57%), a 40% reduction in serum cholesterol and a 35% reduction in serum triaglycerides. It is not sufficiently studied by what mechanisms garlic works to reduce hyperglycemia. The hypoglycaemic effect could be due to an increase in pancreatic insulin secretion from beta cells or an increase in insulin sensitivity (Thomson *et al.,* 2007). Another proposed mechanism is that the antioxidant effect of S-allycysteine sulfoxide (an isolated product from garlic) may contribute to the antidiabetic effects of garlic (Augusti and Sheela, 1996). According to another study, garlic is thought to function as an antidiabetic agent by increasing the secretion of pancreatic insulin from beta cells or the release of bound insulin (Jain and Vyas, 1975).

3. *Anacardium occidentale* L.

The hypoglycemic effect of *Anacardium occidentale* was observed in a study in Wistar rats in which streptozocin-induced diabetes (STZ) was induced. Rats given oral leaf extract (35, 175, 250 mg/kg) showed a decrease in blood glucose levels. The maximum reduction in blood glucose (37 and 35 %) was observed 180 minutes after administration, at doses of 175 and 250 mg/kg. The extract may act by directly stimulating insulin secretion (Sokeng *et al.*, 2007), or the effect of the extract may include insulin-like extrapancreatic mechanisms such as the stimulation of glucose utilisation and the reduction of hepatic gluconeogenesis (Ali *et al.,* 1993; Gray *et al.,* 2000).

Other studies such as (Kamtchouing *et* al., 1998; Lawrence *et al.*, 2005; Jaiswal *et al.,* 2017) also confirm that *A. occidentale* has demonstrable antidiabetic properties and may be a promising plant species in the treatment of diabetes.

4. *Nasturtium officinale* W.T. Aiton

A study performed on STZ-induced diabetic rats confirmed that oral administration of various concentrations of *Nasturtium officinale* extracts (ethyl acetate, methanol, aqueous) for one week has positive effects on lowering blood glucose. This reduction was comparable to the antidiabetic drug glibenclamide (Hoseini *et al.*, 2009). The hypoglycemic effect of *N. officinale* is also confirmed by studies in diabetic mice, where there was a significant reduction in blood glucose after administration of a hydroalcoholic extract (Romina and Norozi, 2009).

A possible mechanism for the hypoglycaemic effect of *N. officinale* may be to stimulate the islets of Langerhans, to improve peripheral sensitivity to residual insulin and to antioxidant properties (Mousa *et al.,* 2015). Other studies have also shown that N. officinale extract acts as an antioxidant (Ozen, 2009), or its dietary supplementation reduces DNA damage to lymphocytes and corrects the state of antioxidants in the blood of healthy adults (Gill *et al.,* 2007). The hypoglycaemic effect may be due to its antioxidant properties and to prevent streptozocin-induced oxidative stress. Thus, N. officinale protects beta cells, which leads to increased insulin secretion and lowers elevated blood glucose levels (Mousa *et al.,* 2015).

5. *Opuntia ficus-indica* (L.) Mill

A clinical study in Mexico confirmed that ingestion of *Opuntia ficus-indica* has low glycemic, insulinemic and glucose-dependent insulinotropic peptide indices (GIP) and is a suitable agent for patients with type II diabetes without any side effects. The inclusion of this medicinal plant in a high-carbohydrate breakfast or in high soy protein (HSBP) has anthohergic and antihyperinsulin effects and even prevented postprandial blood glucose peaks in HSPB. Its consumption also increased the antioxidant activity (López-Romero *et al.*, 2014). This agrees with the results of a study performed on diabetic rats induced by low doses of STZ. The rats were fed a high fat diet and supplemented with aqueous extract / dry powder for research purposes. The results show that *O. ficus-indica* significantly lowers blood glucose levels (Hwang *et al.*, 2017).

The hypoglycaemic effects of *O. ficus indica* stems were studied in a clinical study involving 8 patients with non-insulin dependent diabetes mellitus. Stems in various modifications (entire boiled, blender boiled, blended crude, blended crude heated at 60°C were administered in a dose of 500g. Glucose levels were measured after 0, 30, 60, 120 and 180 minutes. The results of the study show that blood glucose decreased in all patients, especially 120 and 180 minutes after ingestion of *O. ficus indica*, regardless of the method of preparation (Frati *et al,* 1990).

Effects of cactus pear seed oil (CPSO) extracted from the seeds of O. ficus indica were observed in a study in alloxan-induced diabetic rats. Oral administration of CSPO has been shown to prevent the diabetogenic effect of alloxan, presumably due to the presence of antioxidant compounds. These compounds quench the free radicals produced by alloxan and prevent tissue injury in pancreatic β-cells (Berraaouan *et al.*, 2015).

6. *Artemisia absinthium* L.

The hypoglycemic effects on diabetes of *Artemisia absinthium* extract were demonstrated in a study in rats in which diabetes was induced by alloxan. The most significant results were with high doses of the extract (500 and 1000 mg/kg), which significantly reduced blood glucose levels and the results were comparable to glibenclamide treatment. The extract has also been shown to prevent weight loss and improve the biochemical parameters associated with D. mellitus, such as total cholesterol, urea, creatinine and serum protein. The exact mechanism of antidiabetic effects is unknown. Antihyperglycemic activity may be due to the presence of active ingredients such as α- and beta-thujones, thujyl alcohol, azulenes, bisabolene, cadinene, sabinene, pinene and phellandrene. The main component of A. absinthium is thujone, which is the active ingredient in many other medicinal plants with an effect on insulin sensitization (Daradka *et al.*, 2014).

7. *Baccharis genistelloides* (Lam.) Pers.

The hypoglycemic effect of *Baccharis genistelloides* was demonstrated in rats with streptozotocin-induced diabetes. The rats were treated for 7 days and twice a day with 2000 mg/kg body weight, with an aqueous fraction of ethanolic extract of *B. genistelloides* (Oliveira *et al*, 2005; Barbosa *et al*, 2005). A similar result was obtained in healthy rats treated with aqueous extract of *B. genistelloides*, with a dose of 4.2 mg/kg, for 37 days. A reduction was observed not only in blood glucose but also in serum triglyceride levels (Coelho *et al.*, 2004).

The flavonoids epicatechin and quercetin, which are found in the plant, have proven antidiabetic properties by influencing the mechanisms of insulin resistance (Costa-Gil and Spinedi, 2017). Flavonoids are responsible for the antioxidant properties and thus improve the fact that *B. genistelloides* is a suitable medicinal plant in the treatment of diabetes (Llaure-Mora *et al.,* 2021).

8. *Cynara cardunculus* L.

The antidiabetic activity of *Cynara cardunculus* was addressed in a study performed in STZ-induced diabetic rats. It has been found that the plant extract is rich in polyphenols and thus has an antioxidant and anti-glycation effect. Daily oral administration of *C. cardunculus* extract has also been shown to significantly lower glycemia, and improvements in vascular dilatation functions in diabetic animals have been shown after experiments on isolated aortas. The mechanism by which a plant may be involved in the regulation of glycaemia is its antihyperglycaemic effects (Nazni *et al.,* 2006; Fantini *et al.,* 2011; Heidarian and Soofiniya, 2011), but the exact mechanism is not described. However, it can be assumed that the high feed content in *C. cardunculus* improves satiety and thus indirectly lowers blood glucose. Chlorogenic acid derivatives are the most important substances with antidiabetic effects. *C. cardunculus* also showed good anti-glucosidase, anti-glycation and antihyperglycemic effects (Kuczmannová *et al.*, 2016).

9. *Smallanthus sonchifolius* (Poepp.) H.Rob.

For the treatment of diabetes, tuberous roots and leaves are used from *Smallanthus sonchifolius* (Gonzales De La Cruz *et al.*, 2014; Bussmann and Sharon, 2016). The hypoglycemic activity of "yacón" leaves was demonstrated in laboratory studies with healthy and diabetic rats. Diabetes in rodents was induced by streptozotocin (STZ). Aqueous leaf extracts (tea/decoction) reduce glucose levels and increase plasma insulin levels (Aybar *et al.*, 2001). In other studies, the antidiabetic activity of "yacón" leaves was investigated by tests of inhibition of the activity of α-amylase and α-glucosidase. According to the results obtained, expressed as LC50 in mg/ml, the methanolic extracts of "yacón" leaves are stronger inhibitors of α-amylase ($IC50 = 0.26 \pm 0.02$ mg/ml) than of α-glucosidase ($IC50 = 1.30 \pm 0.04$ mg/ml) (Russo *et al.*, 2015).

10. *Schkuhria pinnata* (Lam.) Kuntze ex Thell.

In a study conducted to validate hypoglycemic activity by evaluating the inhibitory effects on carbohydrate hydrolyzing enzymes: α-glucosidase and α-amylase, it was concluded that the species *S. pinnata* showed hypoglycemic activity *in vitro* although it is not recommended in the treatment of chronic disease due to the toxicity found (Deutschländer *et al.*, 2009). The main phytocompounds of *S. pinnata* are phenols and flavonoids, which have proven numerous therapeutic effects for inflammation and diabetes and have also been shown to be significant in their antioxidant properties (Brian *et al.,* 2019).

11. *Stevia rebaudiana* (Bertoni) Bertoni

The chemical composition of stevia leaves contains a high amount of total phenols, which is a positive indication for antioxidant and antidiabetic properties. Through *in vitro* and *in vivo* (STZ-induced rats) studies, it has been shown that consumption of stevia leaves can prevent or alleviate polydipsia, polyphagia and polyurea. According to the results, long-term use of stevia (1 year) also has the ability to improve glucose tolerance and increase cellular sensitivity to insulin (Shivanna *et al.*, 2013). The most used and extracted substances are stevioside, rebaudioside A, rebaudioside C and dulcoside (Lemus-Mondaca *et al.,* 2012; Yadav and Guleria, 2012).

The antidiabetic effects of stevia are also considered to be its antioxidant properties, for which phenols are primarily responsible. (*S. rebaudiana* has a phenol content of up to 91 mg/g) and its leaves have the ability to scavenge free radicals and prevent lipid peroxidation (Nabilatul *et al.,* 2013).

12. *Erythroxylum coca* Lam.

A hypoglycemic effect popularly called coca was studied in Bolivia, in which 90 patients without a personal pathological history were selected. *Erythroxylum coca* leaves (5 g) were administered as an infusion ("mate") and chewed. The results of the postprandial glycemic patients of the control group (the group that did not eat *E. coca* leaves in any form) were 100.4 (± 11.9) mg, while the values of 82.07 (± 8.8) mg were measured in the patients who chewed coca and in the infusion form 81.8 (± 7.5) mg, indicating that *E. coca* has a positive effect on lowering postprandial glycaemia (Pedro and Revilla, 2013).

13. *Otholobium pubescens* (Poir.) J.W.Grimes

Bakuchiol (meroterpenoid isolated from the leaves) was isolated from the extract by biologically determined fractionation for diabetes type 2 and tested for its effect on diabetic streptozotocin-induced rats. The results show that *Otholobium pubescens* has dose-dependent antidiabetic properties (the best results are 150 mg/kg) and significantly lowers plasma glucose and low triglyceride levels (Krenisky *et al.*, 1999).

14. *Prosopis ruscifolia* Griseb.

The antidiabetic effects of *Prosopis ruscifolia* are confirmed by studies in Wistar rats in which diabetes was induced by alloxan. The results showed that the administration of the hydroalcoholic extract of *P. ruscifolia* significantly reduced the blood glucose level in hyperglycemic rats during acute and chronic treatment and did not show high toxicity. *P. ruscifolia* contains saponins, flavonoids and alkaloids, which are probably responsible for antidiabetic properties (Campuzano-Bublitz *et al.*, 2016). They are an important regulator of oxidative stress, so they serve as antioxidants (Campuzano-Bublitz *et al.,* 2019).

15. *Linum usitatissimum* L.

Flaxseed (*Linum usitatissimum*) is a functional food rich in omega 3 fatty acids and low carbohydrate antioxidants. The *L. usitatissimum* extract was administered as a dietary supplement to study participants (10 g for 1 month), the results of which were evaluated on the basis of clinical-biochemical parameters. Flaxseed supplementation has been shown to have a positive effect on lowering blood glucose (19.7 % reduction) and glycated hemoglobin (15.6 %). The addition of the extract also had an effect on total cholesterol (a decrease of 14.3 %) and triglycerides (17.5 %) (Mani *et al.*, 2011). Other studies such as (Kaur *et al.*, 2017; Bouzghaya *et al.*, 2020) also show that *L. usitatissimum* has significant antidiabetic properties.

16. *Swietenia macrophylla* King

Swietenin, tetranortriterpenoid isolated from *Swietenia macrophylla* seeds, was orally administered daily to diabetic streptozotocin-induced rats at doses of 25 and 50 mg/kg. The study showed that swietenin treatment significantly reduced blood glucose levels (fasting) and also contributed to lowering elevated cholesterol, triglycerides and improving liver glycogen levels (Dewanjee *et al.*, 2009). The *S. macrophylla* phytochemical test indicated the presence of triterpenoids in the methanol extract, which may serve as potential hypoglycemic agents (Maiti *et al.,* 2008).

17. *Abuta grandifolia* (Mart.) Sandwith

The species was scientifically determined the reducing efficacy of blood glucose level in rats with induced diabetes with *Abuta grandifolia* aqueous extract. The aqueous extract obtained from the bark of this species was supplied to the rats orally in a dose of 250 mg/kg, for 4 days (Justil *et al.*, 2015). Another study in alloxan-induced diabetic rats shows that *A. grandifolia* extract administration has a hypoglycemic effect and no antihyperglycemic effect. However, it showed a significant antihyperglycaemic effect in healthy rats (Díaz Cabanillas *et al.,* 2019). The presence of alkaloids and isolated berberine derivatives, which result in the expression of insulin receptors and improved glucose utility, have been detected in this medicinal plant (Justil *et al.,* 2015).

18. *Eucalyptus globulus* Labill.

A significant hypoglycaemic effect was observed in stretozocoin-induced diabetic rats. A dose of the aqueous extract (150 and 300 mg/kg body weight) of *Eucalyptus globulus* was administered once or repeatedly. The results of the study show that the aqueous extract has a significant and dose-dependent effect on blood glucose levels (Jouad *et al.*, 2004). This agrees with other study that also identify *E. globulus* as a suitable adjunct in the treatment of diabetes mellitus in traditional medicine (Eidi *et al.*, 2009). Antihyperglycemic activity is likely to be associated with insulin stimulation and improved muscle glucose absorption and metabolism. The main chemical components are eucalyptol (cineole), terpineol, isoamyl alcohol, tannins, terpenes, sesquiterpene, ethanol, aliphatic aldehydes, dioxane, ligin and catechin, which are responsible for antidiabetic activities (Jouad *et al.,* 2004).

19. *Psidium guajava* L.

According to the results of the study, butanol extract from *Psidium guajava* leaves has positive effects in diabetic mice on the treatment and prevention of glycemia associated with type 2 diabetes. It has been shown to be effective in inhibiting PTP1B (protein tyrosine phosphatase 1B), which is a major mediator of insulin signaling and insulin resistance (Oh *et al.*, 2005). Also other studies focusing on the antidiabetic properties of *P. guajava* also confirm that plant extracts are a suitable supplement in the treatment of diabetes (Shen *et al.*, 2008; Rai *et al.*, 2010; Huang *et al.*, 2011).

20. *Passiflora mollissima* (Kunth) L.H. Bailey

Ethanolic extract from the leaves and aerial parts of *Passiflora mollissima* was administered to alloxan-induced diabetic rats. The experiment showed that treatment with *P. mollissima* extract had a significant effect on lowering sugar levels in hyperglycemic animals. Blood glucose lowering activity may be due to inhibition of renal glucose reabsorption or stimulation of insulin release (Edwin *et al.*, 2007).

21. *Sesamum indicum* L.

A nephroprotective and antidiabetic effects were shown in a study in streptozotocin-induced diabetic rats given ethanol extract of *Sesamum indicum* seeds for 8 weeks. The results showed that STZ-induced diabetic rats showed a significant reduction in serum protein, creatinine and urea levels, which are among the basic biochemical parameters in renal damage associated with diabetes mellitus. The results further suggest that ethanol seed extract has a potential effect on the control and treatment of hyperglycemia (Bhuvaneswari and Krishnakumari, 2012). One mechanism may be (+) - pinoresinol as a hypoglycemic agent (Wikul *et al.,* 2012).

22. *Rubus fruticosus* L.

The effect of hydroethanolic extracts of *Rubus fruticocus* was studied on STZ-induced diabetic Wistar rats. The extract was administered at doses of 50, 100 and 200 mg/kg for 4 weeks, at which end samples were taken to measure malondialdehyde, glutathione and total oxidation status. The study concludes that diabetes causes oxidative damage and subsequent serum levels of inflammation, and *R. fruticocus* may have potential antidiabetic properties, mainly due to its high content of antioxidants (Mirazi and Hosseini, 2020). The substances responsible for these properties may be anthocyanins (flavonoid derivatives) found in this fruit (Zia-UI-Haq *et al.,* 2014).

23. *Coffea arabica* L.

Coffee, as the second most popular beverage in the world (George *et al.*, 2008), is known for its antioxidant properties. Her antidiabetic properties were studied in diabetic rats, in which they were given an aqueous extract of coffee green beans (63 and 93 mg/kg) once a day for 15 days. Diabetic rats showed significantly lower blood glucose levels at the end of the aqueous extract course and are thus a potential means of relieving diabetes hyperglycemia (Campos-Florián *et al.*, 2013). The most important bioactive ingredient is chlorogenic acid, which is associated with antioxidant and anti-inflammatory properties. In addition, it can reduce insulin resistance and reduce hyperglycemic levels targeting hepatic glucose metabolism (Wafa *et al.,* 2020).

24. *Citrus medica* L.

The antidiabetic, hypocholesterolemic and hypolipidemic activities of *Citrus medica* are confirmed by studies in rats treated with ether seed extract. The results showed a significant reduction in fasting blood glucose, serum cholesterol and serum triglycerides (Sah *et al.*, 2011).

25. *Aloe vera* (L.) Burm.f.

The antioxidant properties of *Aloe vera* were studied in diabetic rats. *A. vera* gel was administered orally at a concentration of 300 mg/kg. After the treatment, there was a significant reduction in blood glucose levels, as well as glycosylated hemoglobin. Increased levels of lipid and hydroperoxide peroxidation in tissues returned to normal values. *A. vera* gel treatment also resulted in increased glutathione, superoxide dismutase, catalase and glutathione-S-transferase in the liver and kidney. Thus, the results confirm the clear antioxidant property of the *A. vera* gel, and even this treatment was more successful than the treatment with glibenclamide (Rjasekaran *et al.*, 2005).

2.5. Conclusions

The present review demonstrates that there is a great diversity of plant species used by the population of Bolivia for the treatment of the symptoms related to diabetes mellitus type II, according to ethnobotanical studies of medicinal plants carried out in recent years, 35 species with antidiabetic activity are used. Scientific studies show the antidiabetic activity for most of the plants used in traditional medicine in Bolivia. The information obtained can give some clues for future analyses in order to develop new medications. More biochemical and clinical analysis of medicinal plants is still needed to make better use of their potential.

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3. Conclusions

A few ethnobotanical studies on this topic have been published, but none have been designed as a comprehensive list of medicinal plants used in traditional medicine in Bolivia, and their antidiabetic activity has not been subsequently verified - this is therefore the first paper of its kind.

Traditional medicine is indispensable to Bolivia - it is often the only source of health care, whether due to distrust and distance for rural residents or affordability for urban dwellers. Its importance is also demonstrated by the incorporation of traditional medicine in the national health system by Law No. 459.

Bolivia is geographically rugged and as a result has a great diversity of plants. This makes it a great potential for the search for new medicinal plants and medicinal substances, not only for the treatment of diabetes mellitus.

The trend of diabetes mellitus in Bolivia is still on the rise. This disease costs many lives and, combined with the lack of health care, the condition is becoming almost epidemic. Medicinal plants can greatly help to control this situation, either as a main treatment or as an adjunct to conventional treatment. However, further ethnobotanical studies and other biochemical analyses are required for the proper use of medicinal plants with antidiabetic activity.

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Appendices

List of the Appendices:

Appendix 1 Manuscript: Acknowledgement of acceptance for publication

Blacpma

MS EDITIONS

Boletín Latinoamericano y del Caribe de Plantas Medicinales y Aromáticas

March 10, 2022

Dr.
Eloy Fernández-Cusimamani
Czech University of Life Sciences Prague
Prague
Czech Republic

Dear Dr. Fernández-Cusimamani:

His article entitled: **"Medicinal plants with antidiabetic activity used in the traditional medicine in Bolivia: A review"** (BLACPMA number 2073) by the authors **Lucie Peková, Jana Žiarovská & Eloy Fernández-Cusimamani,** received on August 20, 2021. It has been **accepted** on March 10, 2022 for publication in BLACPMA as a Review.

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Greets you

Jose L. Martinez
BLACPMA Editor in Chief

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