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Revisión / Review

Antidiabetic potential of medicinal plants from the Peruvian Amazon: A review

[Potencial antidiabético de plantas medicinales de la amazonía peruana: Una revisión]

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Abstract: Diabetes mellitus is a metabolic disorder characterized by the presence of chronic hyper-glycemia that is accompanied, to a greater or lesser extent, by alterations in the metabolism of carbohydrates, proteins and lipids. It is the leading cause of death in developed countries. Current antidiabetic drug treatments present several adverse effects for which it has started searching for new oral hypoglycemic agents from vegetal species. This review presents the medicinal plants from the Peruvian Amazon used in the treatment of diabetes and a systematic review of their hypoglycemic properties reported in the literature in the last twenty years used in different bibliographic databases. Seventy seven medicinal plants are reported as being used for the treatment of diabetes by Amazonian indigenous people, which 46.75% of species report hypoglycemic activity, evidencing that traditional knowledge is a great source for to searching antidiabetic drugs and also an alternative for future research.

Keywords: Diabetes; Amazonian species; Pharmacological studies; Traditional uses; Hypoglycemic activity

Resumen: La diabetes mellitus es un trastorno metabólico caracterizado por la presencia de hiperglucemia crónica acompañada, en mayor o menor medida, de alteraciones en el metabolismo de carbohidratos, proteínas y lípidos, es la principal causa de muerte en los países desarrollados. Los tratamientos actuales con fármacos anti-diabéticos presentan varios efectos adversos, por lo que se ha iniciado una búsqueda de nuevos hipoglucemiantes orales a partir de especies vegetales. Esta revisión presenta las plantas medicinales de la amazonia peruana utilizadas en el tratamiento de la diabetes y una revisión sistemática de sus propiedades hipoglucémicas reportadas en la literatura en los últimos veinte años utilizando bases de datos bibliográficas. Se reportan 77 plantas medicinales utilizadas para el tratamiento de la diabetes por pobladores amazónicos, de las cuales el 46.75% reporta actividad hipoglucémica, evidenciando que el conocimiento tradicional es una fuente para la búsqueda de fármacos antidiabéticos y una alternativa para futuras investigaciones.

Palabras clave: Diabetes; Especies amazónicas; Estudios farmacológicos; Usos tradicionales; Actividad hipoglucemiante

INTRODUCTION

Diabetes mellitus is a metabolic disorder considered a common chronic disease that is becoming a serious threat to humanity's health. The prevalence of diabetes mellitus is expected to reach up to 10,2% (578 million) in the world by 2030 (Saeedi *et al*., 2019). Among all types of diabetes, type 2 diabetes mellitus (T2DM) is the main complication and most frequent clinical form of diabetes, accounting for approximately 90% of reported cases (Furrianca *et al*., 2015; Patel *et al*., 2012). Moreover, diabetes mellitus has been cataloged as the epidemic of the 21st Century, both because of its increasing magnitude and its impact on cardiovascular disease, being the last considered as the leading cause of death in developed countries (Valdés *et al*., 2007). Like many chronic non-communicable diseases, which require long-term treatment and other care to prevent complications and negative outcomes, diabetes represents a high cost to society and health systems (Chow *et al*., 2018). The high prevalence and long-term complications of diabetes mellitus combined with the side effects of antidiabetic drugs have started an intense search for new oral hypoglycemic agents from plants used in traditional medicine for the treatment of this pathology, especially in developing countries where resources are scarce and medical plants play an important role in the management of this disease (Surya *et al*., 2014).

Population studies in Peru indicate that the prevalence of diabetes has increased and approximately two new cases are registered for one hundred people a year (Carrillo-Larco & Bernabé-Ortiz, 2019). People with diabetes are more likely to develop more severe clinical forms of Covid-19 infection and there is an association between diabetes and admission to the intensive care unit (García *et al*., 2020).

Plants that are traditionally used for the treatment of diseases have constituted from ancient times a source to cover the therapeutic needs, being their scientific validation necessary to corroborate their uses and toxicity effects (Vásquez-Ocmín *et al*., 2018). Medicinal plant studies have become a universal scientific fact that transcends not only for the benefits on health but also for the productivity and the economic system of a country (Muñoz *et al*., 2001). Moreover, medicinal plants constitute an important resource to indigenous people, who often lack access to conventional health care systems either due to isolation or to economy. This is a common condition in developing countries. Many Amazonian ethnic groups have practiced consistent application of different plant species for various ailments for millennia and have transmitted this long-term experience from one generation to the next (Desmarchelier & Schaus, 2000). But native people are not the only ones who have a detailed knowledge of the local Amazonian ecosystems in which they live. The long-term residents of the Amazon also do so. There is many mestizo communities in the Amazon that depend on traditional medicine as their sole source of medical care, due to tradition and lower price than the cost of Western therapy. It is believed that the traditional knowledge of mestizos may have been adopted from extinct or endangered indigenous cultures (Jovel *et al*., 1996).

There are many medicinal plants to be useful in diabetes treatment and have been used empirically as antidiabetic and anti-hyperlipidemic remedies (Malviya *et al*., 2010; Mirhoseini *et al*., 2013; Sekar *et al*., 2014). According to Preethi (2013), more than 800 plant species from all over the world have hypoglycemic effects. Previous reviews have shown the importance and the interest to demonstrate the antidiabetic effects of plants and to isolate bioactive agents from medicinal plants around the world (Grover *et al*., 2002; Hasani-Ranjbar *et al*., 2008; Kavishankar *et al*., 2011; Patel *et al*., 2012; Arumugam *et al*., 2013). In most of the studies, natural products mainly derived from plants have been tested in diabetes models induced by chemical agents. Most experiments in diabetes are carried out on rodents, although some studies are still performed on larger animals (Fröde & Medeiros, 2008).

One of the countries with the greatest biodiversity in the world is Peru, with an estimated flora of approximately 25,000 species, 10% of the world's flora grows in Peru and 30% of the species are endemic. It is estimated that the population uses approximately 5,000 Peruvian plants for 49 different purposes and uses (Vásquez-Ocmín *et al*., 2018). Furthermore, the Peruvian Amazon flora is one of the largest reserves of phytotherapeutic resources and the use of medicinal plants is a common practice (Mejía & Rengifo, 2000). Despite this tradition, there is little documented information about the practical aspects of the use of medicinal plants and their scientific validations published.

This review shows plant species used in folk medicine for the treatment of diabetes in the Peruvian Amazon complemented with experimental studies performed on hypoglycemic effect or antidiabetic activity of those plants where their ethnomedical uses have been validated, or close to validation. This is the first such review that focuses on the efficacy and safety of Peruvian Amazon plants in the management of diabetes.

MATERIALS AND METHODS

The selection of vegetable species from the Peruvian Amazon with traditional use for diabetes treatment were made taking into account the information reported by Flores (1984), Vásquez (1992), Jovel *et al*. (1996), Mejía & Rengifo (2000), Rengifo-Salgado (2007), Rutter (2008), Sanz-Biset *et al*. (2009) and Polesna *et al*. (2011), Huaranca *et al*. (2013), Bussmann & Sharon (2016), complemented with the database of medicinal plants of Instituto de Investigaciones de la Amazonía Peruana (IIAP, 2010). Then a search for papers published in the last twenty years on the antidiabetic potential of the selected species was carried out, through a systematic review in the following bibliographic databases: MEDLINE, Web of Science, SCOPUS, Wiley, PubMed and Scielo, using Boolean operators in the following search strategy: combining keywords such as the scientific name of the plant and "diabetes", "hypo-glycaemic activity" "antidiabetic", "Amazonian plants" "hypoglycemic and "Anti-hyperglycemic" and/or medicinal tropical plants.

RESULTS

Ethnopharmacological knowledge

Table No. 1 shows a review of the species from the Peruvian amazon used in the treatment of diabetes, for each species its family, common name, part of the plant used, the way of preparation have been described and a summary of the pharmacological studies carried out. Likewise, we have indicated (*) the species of antidiabetic use for which no reports about their antidiabetic activity have been found in the databases.

Table No. 1
Medicinal plants from the Peruvian Amazon used for traditional treatment of diabetes

Scientific name	Family	Common name	Plant parts used	Preparation	Pharmacological studies
Abuta grandifolia	Menispermaceae	Abuta, motelo sanango	Bark, Trunk	Decoction, maceration	Hypoglycemic effect
*Acmella oppositifolia**	Asteraceae	Botón de oro, botoncillo	Aerial part	Infusion	-----
Agropyron repens	Poaceae	Grama	Leaves /aerial part	Infusion	Hypoglycemic effect
*Alternanthera halimifolia**	Amaranthaceae	Sanguinaria, yerba blanca, ojo de pollo, picurillo	Aerial part	Infusion	-----
*Amburana cearensis**	Fabaceae	Ishpingo colorado	Bark	Decoction	-----
Anacardium occidentale	Anacardiaceae	Caso, cashú, marañon	Bark	Decoction	Enzymatic activity, hypoglycemic activity, antidiabetic activity
Annona muricata	Annonaceae	Guanábana	Leaves, bark	Decoction, Infusion	Clinical trial, antidiabetic activity, hypoglycemic activity, enzymatic activity
*Annona cordifolia**	Annonaceae	Anunilla, waska	Leaves, bark	Decoction	Antidiabetic effect
*Arrabidaea chica**	Bignoniaceae	Puca panga	Leaves	Decoction	-----
Artocarpus altilis	Moraceae	Pan del árbol	Bark	Infusion	Antidiabetic effect, enzymatic activity
*Aspidosperma nitidum**	Apocynaceae	Pinshi caspi, quillobordón, jacamin, remo caspi	Bark	Infusion	-----
Averrhoa carambola	Oxalidaceae	Carambola	Fruit / Leaves	Infusion	Hypoglycemic activity, anti-

					hyperglycemic activity
*Bauhinia glabra**	Fabaceae	Escalera de mono, pata de vaca	Leaves	Decoction	-----
*Baccharis salicifolia**	Asteraceae	Hierba de la plata, chilco hembra	Whole plant	Decoction	-----
Bertholletia excelsa	Lecythidaceae	Castaña	Leaves	Decoction	Anti-hyperglycemic effect
Bidens pilosa	Asteraceae	Amor seco, cadillo	Leaves/aerial part	Decoction	Enzymatic activity, anti-hyperglycemic effect, antidiabetic effect
*Bowdichia virgilioides**	Fabaceae	Alcornoque	Seeds	Infusion	-----
*Brosimum rubescens**	Moraceae	Palo sangre	Bark/wood	Decoction	-----
Cajanus cajan	Fabaceae	Puspo poroto	Leaves	Decoction	Hypoglycemic effect, anti-hyperglycemic effect, antidiabetic activity
*Calycophyllum spruceanum**	Rubiaceae	Capirona	Bark	Decoction	-----
*Catharathus roseus**	Apocynaceae	Isabelita, clavel rosado, clavel blanco	Flowers	Decoction	-----
Cecropia obtusifolia	Urticaceae	Cetico	Leaves	Decoction	Clinical trial, hypoglycemic effect
*Chenopodium ambrosioides**	Amaranthaceae	Paico	Aerial part	Decoction	-----
Citrus máxima	Rutaceae	Limón	Fruit	Juice	Antidiabetic effect, antidiabetic activity, anti-hyperglycemic activity
*Cnidoscolus urens**	Euphorbiaceae	Pringamoza, Angel tauna, guartiro	Leaves	Infusion	----
Coffea arabica	Rubiaceae	Café	Fruit/ Leaves	Infusion	Antidiabetic effect
*Cyclanthera pedata**	Cucurbitaceae	Caigua	Fruit	Fresh	-----
Cymbopogon citratus	Poaceae	Hierva luisa	Leaves	Infusion	Antidiabetic effect, hypoglycemic effect
*Dioscorea trifida**	Dioscoreaceae	Sacha papa morada	Tubercle	Decoction	-----
*Eriochloa polystachya**	Poaceae	Hierva caribe	Leaves	Infusion	-----
Eryngium foetidum	Apiaceae	Sacha culantro	Aerial part	Decoction	Antidiabetic potential
Euterpe oleracea	Arecaceae	Huasaí	Seed	Infusion	Antidiabetic effect
*Euterpe precatoria**	Arecaceae	Huasí	Roots	Decoction	-----
Gomphrena globosa	Amaranthaceae	Siempre viva, perpetua violeta, manto de cristo	Flowers	Infusion	Hypoglycemic effect
Guazuma ulmifolia	Malvaceae	Bolaina negra	Bark / Leaves	Infusion	Clinical trial, antidiabetic activity
*Ilex guayusa**	Aquifoliaceae	Guayusa, agracejo, citrodora	Leaves	Infusion	-----
*Iriartella setigera**	Arecaceae	Ponilla	Fruits	Infusion	-----
*Irlbachia alata**	Gentianaceae	Campanita	Flowers	Infusion	-----

*Juglans neotropica**	Junglandaceae	Nogal	Leaves	Infusion	-----
Lantana cámara	Verbenaceae	Sacha orégano	Leaves	Infusion	Enzymatic activity, antidiabetic potential, anti-hyperglicemic activity
*Macrolobium acaciifolium**	Fabaceae	Ari pari	Leaves	Infusion	-----
Momordica charantia	Cucurbitaceae	Papailla	Leaves / fruits	Decoction / fresh	Clinical trial, hypoglycemic effect, antidiabetic activity, enzymatic activity
Musa paradisiaca	Musaceae	Plátano	Flowers	Decoction	Anti-hyperglycemic activity, hypoglycemic effect
Myrciaria dubia	Myrtaceae	Camu camu	Fruits	Infusion	Antidiabetic activity, anti-hyperglycemic property, enzymatic activity
*Pachira aquatica**	Malvaceae	Sacha pandisho	Bark	Decoction	-----
*Passiflora laurifolia**	Passifloraceae	Granadilla amazónica	Leaves	Decoction	-----
*Passiflora quadrangularis**	Passifloraceae	Tumbo	Leaves	Decoction	-----
Peperomia pellucida	Piperaceae	Lengua de motelo	Aerial part	Decoction	Hypoglycemic activity
Persea americana	Lauraceae	Palta	Leaves	Decoction	Antidiabetic activity
Petiveria alliacea	Phytolaccaceae	Mucura hembra	Leaves	Decoction	Hypoglycemic activity
*Phthirusa pyrifolia**	Loranthaceae	Suelda con suelda	Leaves	Decoction	-----
Phyllanthus niruri	Phyllanthaceae	Chanca piedra blanca	Aerial part	Infusion	Antidiabetes activity
Phyllanthus urinaria	Phyllanthaceae	Chanca piedra	Aerial part	Infusion	Antidiabetic activity
Physalis angulata	Solanaceae	Bolsa mullaca	Leaves / root	Decoction /maceration	Antidiabetic activity
*Piper hispidum**	Piperaceae	Cordoncillo	Leaves	Decoction	-----
*Pithecellobium mathewsii**	Fabaceae	Algarrobo, jonosh	Fruit	Decoction	-----
Plantago major	Plantaginaceae	Llantén	Leaves	Decoction	Enzymatic activity, hypoglycemic effect, antidiabetic activity
*Polypodium angustifolium**	Polypodiaceae	Calahuala	Rhizomes	Decoction	-----
Portulaca oleracea	Portulacaceae	Verdolaga	Aerial part	Infusión/ fresh	Enzymatic activity, Anti-hyperglycemic activity, antidiabetic activity
*Rauvolfia tetraphylla**	Apocynaceae	Sanango	Leaves	Infusion	-----
*Ruellia tuberosa**	Acanthaceae	Mechati rao, yuca de puerco	Root	Infusion	-----
Scoparia dulcis	Plantaginaceae	Ñucño pichana	Whole plant	Infusion	Antidiabetic activity, hypoglycemic activity, shows no enzimatic activity

Senna reticulata	Fabaceae	Retama	Flores	Infusion	Hypoglycemic effect
*Serjania brachyptera**	Sapindaceae	Huarate	Stem	Decoction	-----
Solanum sessiliflorum	Solanaceae	Cocona	Fruit	Decoction / fresh	Hypoglycemic effect
Stachytarpheta cayennensis	Verbenaceae	Verbena negra	Leaves	Decoction	Hypoglycemic activity
Syzygium cumini	Myrtaceae	Aceituna dulce	Fruit	Infusion	Antidiabetic effect, hypoglicemic effect, anti-hyperglicemic activity
*Tabebuia incana**	Bignoniaceae	Tahuari	Bark	Decoction	-----
*Tabebuia obscura**	Bignoniaceae	Tahuari oscuro	Bark	Decoction	-----
*Tabebuia serratifolia**	Bignoniaceae	Tahuari	Bark	Decoction	-----
Terminalia catappa	Combretaceae	Castanilla	Leaves	Infusion	Antidiabetic effect
*Theobroma subincanum**	Malvaceae	Cacao del monte	Leaves	Infusion	-----
*Tynanthus panurensis**	Bignoniaceae	Clavo huasca	Bark	Maceration / decoction	-----
*Uncaria guianensis**	Rubiaceae	Uña de gato	Bark	Decoction	-----
Uncaria tomentosa	Rubiaceae	Uña de gato	Bark	Decoction	Hypoglycemic effect
*Urera baccifera**	Urticaceae	Mara - mara	Leaves	Infusion	-----
*Verbena litoralis**	Verbenaceae	Verbena, verbena negra	Leaves	Infusion /crushed	-----

Seventy seven plants are reported for the treatment of diabetes mellitus in the Peruvian Amazon. The families with more recorded species to manage of this pathology are Fabaceae (7), Bignoniaceae (5), Rubiaceae (4) Amaranthaceae (3), Poaceae (3), Apocynaceae (3), Arecaceae (3), Verbenaceae (3), Asteraceae (3) and Malvaceae (3). Of the reports species 46.75% (36) of them have presented reports in scientific research databases that support their use as antidiabetic from the point of view of their biological activity.

Pharmacological studies

The reports of pharmacological studies of extract and fractions that demonstrate the scientific support of the plants used to treat diabetes in the Peruvian Amazon are described below. Plants which did not show any significant hypoglycemic effect were not included.

Abuta grandifolia

The hypoglycemic effect of *A. grandifolia* bark in alloxan-induced diabetic rats was evaluated. The administration of the hydroalcoholic extract in a single dose of 250 mg/Kg body weight caused a 42.05% and 14.67% reduction in serum glucose levels, after 2 and 8 hours of treatment, respectively (Cabanillas *et al*., 2019).

The hypoglycemic activity of aqueous extract of the *A. grandifoli*a bark in alloxan induced diabetic rats was evaluated. Oral doses of extract (250 mg/kg) and glybenclamide (10 mg/kg) showed a decreasing blood glucose by 26.9% and 26.4% respectively, after 24 hours of treatment (Justil *et al*., 2015).

Agropyron repens

The hypoglycemic effect of an aqueous extract of *A. repens* rhizomes was investigated in streptozotocin-induced diabetic rats. After a single oral administration of the aqueous extract (20 mg/kg) a significant decrease on blood glucose levels in streptozotocin diabetic rats was observed; the blood glucose levels were normalized after 2 weeks of daily oral administration of aqueous extract (20 mg/kg) (Eddouks *et al*., 2005).

Anacardium occidentale

Many studies have been reported about its antidiabetic activity. Some relevance studies are shown below.

The inhibitory potential of the aqueous extract of *A. occidentale* leaves on the carbohydrate digestive enzymes *in vivo* was investigated. The extract co-administered to normoglycaemic rats with starch for the α-amylase and maltose or sucrose for the maltase and sucrase, respectively. There was a 37.8%, 28.9% and 23.8% increase in blood glucose concentrations after 30 minutes of starch, maltose and sucrose administration respectively. For the same time interval, 200 mg/kg dose of the aqueous extract of *A. occidentale* co-administered with the starch, completely inhibited the glucose concentration rise, unlike when co-administered with maltose and sucrose the extract showed an increase in blood glucose concentration of 18.8% and 43.9%, respectively. Acarbose use as standard drug (100 mg/kg) also completely inhibited the glucose concentration rise when co-administered with starch while with maltose and saccharose, a light increase in blood glucose concentration of 2.3% and 11.3% respectively (Gidado *et al*., 2019) was shown.

The hypoglycemic activity of hydroalcoholic extract from leaves and bark of *A. occidentale* by the 40% glucose induced test in rats was evaluated. The evaluation of hypoglycemic activity showed that leaves extract (750 mg/kg) behaves similarly to metformin (500 mg/kg) while that bark extract did not show to have hypoglycemic activity (Japón *et al*., 2017).

The antidiabetic activity of ethanol extract of *A. occidentale* leaves was evaluated on neonatal streptozotocin diabetic rats. On administration of 100 mg/kg of plant extract, blood glucose levels of the rats showed 8.01% and 19.25% decrease in the fasting blood glucose levels on day 15 and day 30, respectively. For pioglitazone use as standard drug (2 mg/kg) the reduction percentage of blood glucose level was 10.58% and 21.75 on day 15 and day 30, respectively (Jaiswal *et al*., 2016).

The hypoglycemic effect of methanolic extract of *Anacardium occidentale* leaves in alloxan-induced diabetic rats was evaluated. 200 mg/kg dose of extract in moderately diabetic rat (100 and 300 mg/dL of blood glucose) caused a decreased in blood glucose level of 79.2% over four hours while tolbutamide (400 mg/kg) caused a decreased of 63.1% (Fagbohun & Odufunwa, 2010).

The hypoglycemic effect of aqueous extract of *A. occidentale* leaves in alloxan-induced hyper-glycemic rabbits was evaluated. 400 mg/kg dose of extract lowered the mean fasting blood sugar levels showing a percentage maximum reduction was 56.4% while for tolbutamide standard drug (200 mg/kg) the percentage was 85.6% (Esimone *et al*., 2001).

Annona muricata

Numerous scientific investigations have been conducted to study the antidiabetic effects of *A. muricata*. A recently published review on the efficacy of this species in the management of diabetes identified 17 types of studies (1 clinical, 10 *in vivo*, 4 *in vitro*, 1 *in vivo*/*in vitro* and 1 *in silico*). In the clinical study evaluated the adjuvant effect of ethanol extract of *A. muricata* leaves in patients with type 2 diabetes mellitus where patients were given capsules of extract (180 mg), along with 5 mg of glibenclamide for a month. Other group were given glibenclamide only. A greater decrease in blood glucose level was observed in those who received *A. muricata* extract and glibenclamide. *In vivo* studies showed that leaves present better activity than other parts in rodent models. Water and methanol were the most frequently used solvents. The streptozotocin (STZ)-induced diabetic rat was the animal model most used. 100 mg/kg of extract was the most used and effective dose, reducing blood glucose levels by up to 75%. All of the *in vitro* studies demonstrated a significant effect of different part of the plant on inhibition of α-amylase and α-glucosidase activities (Alwan *et al*., 2020). In another study, that was not included in the previous review, the anti-hyperglycemia effects of methanolic extract of *A. muricata* leaves in streptozotocin-induced diabetic mice was investigated. Treatment with a daily dose of methanolic extract (100 mg/kg) for two weeks, reduced blood glucose in mice by 14% additional compared to mice that did not receive (Lestari *et al*., 2019).

Artocarpus altilis

The antidiabetic effects of *A. altilis* leaf powder in alloxan induced diabetic rats was investigated. The animals were fed with a diet formulated using 5% leaf powder for four (4) weeks. There was a remarkable decrease in blood glucose in both the treated and the pre-treated group (Ajayi & Arowolo, 2019).

The α-glucosidase enzyme inhibitory activity of *A. altilis* leaves was studied. The varieties of leaf used were the yellow and green leaves. The ethanol extracts of both yellow and green leaf showed a good enzyme inhibitory activity with IC_{50} of 9.07 and

11.01 ppm, respectively. Meanwhile, the positive control, acarbose showed a strongest inhibitory activity with IC_{50} of 6.79 ppm (Rante *et al*., 2019). In another study, the α-glucosidase enzyme inhibition assay of *A. altilis* leaf extract showed that ethanol extract and ethyl acetate fraction have antidiabetic activity stronger than quercetin as positive control with IC_{50} values of 6.79 μg/mL, 5.98 μg/mL and 11.60 μg/mL, respectively (Lotulung *et al*., 2014).

The effect of the *A. altilis* fruit based-diet on fasting blood glucose level in alloxan induced diabetic rats was investigated. The feeding of the diabetic rats with *A. altilis* fruit for three weeks reduced in blood glucose level by 78.4%, while metformine caused a decreased of 77.8% (Ajiboye *et al*., 2017a).

Averrhoa carambola

The hypoglycemic activity of benzoquinone isolated from the roots of *A carambola* on streptozotocin-induced diabetic mice was evalualed. After 21 days of treatment, a dose of 120 mg/kg of benzoquinone showed the same therapeutic effect as metformin (300 mg/kg) reducing the blood glucose levels compared with the model control group (Qin *et al*., 2020).

The hypoglycemic effects of aqueous extract (juice) of *A. carambola* fruit in streptozotocin-induced diabetic mice was evaluated. After 21 days of treatment, doses of 100, 50 and 25 mg/kg of extract reduced blood glucose levels by 31.20%, 20.33% and 8.34%, respectively; while metformin (320 mg/kg) caused a decreased of 29.80% (Pham *et al*., 2017).

The hypoglycemic effect of hydroalcoholic extract of *A. carambola* root in streptozotocin-induced diabetic mice was studied. A dose of 1200 mg/kg of extract, after 21 days of treatment, significantly decreased the serum levels of blood glucose and elevated the content of serum insulin. These results were very similar to metformin treatment (320 mg/kg) (Xu *et al*., 2014).

The anti-hyperglycemic potential of methanolic extract of *A. carambola* leaves in oral glucose tolerance test with glucose-loaded mice was studied. 400 mg/kg dose of the extract caused a 34.1% reduction in serum glucose levels when compared to control animals. While the standard anti-hyperglycemic drug, glibenclamide (10 mg/kg), caused a 57.3% reduction in serum glucose levels versus control (Shahreen *et al*., 2012).

The potential anti-hyperglycemic effects of the hydroalcoholic extract and EtOAc fraction from *A. carambola* leaves in normal glucose-fed rats was studied. For a time of 30 minutes, a dose of 400 mg/kg of the hydroalcoholic extract and EtOAc fraction co-administered with glucose (4 g/kg) showed an increases serum glucose level of 50.0% and 50.5%, respectively, while the rats that received only glucose-feed were a 64.5% increase serum glucose level. Likewise, the oral hypoglycemic agent, tolbutamide (100 mg/kg), when was co-administered with glucose showed an increase serum glucose level of 58.7%. After 180 min, EtOAc fraction completely inhibited the glucose concentration rise (Cazarolli *et al*., 2012).

Bertholletia excelsa

The anti-hyperglycemic potential of aqueous extract of *B. excelsa* nut in streptozotocin-induced diabetic rats was studied. After 7 days of treatment a daily dosage of 1.1 g of the extract, which corresponds to 50% of the Recommended Dietary Allowance (RDA) for humans adjusted for rats considering average weight of a male human adult (70 kg), significantly decreased the levels of circulating glucose in diabetic animals by 30.95%, this compared with control group (Nascimento *et al*., 2020).

Bidens pilosa

The α-glucosidase inhibitory activity of the *n*-hexane, chloroform and aqueous extract from *Bidens pilosa* leaves was evaluated, exhibiting IC_{50} values of 235.8, 125.6 and 100.3 mg/mL, respectively. In addition, caffeoylquinic acid derivatives were isolated from the aqueous extract, and showed better α-glucosidase inhibitory activity, with IC_{50} values ranging from 10.7 to 74.7 μM, than acarbose that presented IC_{50} value of 214.5 μM (Thien *et al*., 2017).

The anti-hyperglycemic effect of aqueous extract of *B. pilosa* aerial part in blood glucose in *db/db* mice was eavluated. A dose of 250 mg/kg of extract significantly decreased blood glucose levels (32.96%) and increased serum insulin levels in db/db mice (Hsu *et al*., 2009).

The antidiabetic effects of methanol extracts and three polyacetylenic compounds from three variants of *B. pilosa* leaves using db/db mice was studied. All crude extracts and their polyacetylenic active compounds lowered blood glucose levels and elevated insulin levels, being the extract of *B. pilosa* var. *radiata* was the one that had better antidiabetic activities than the extracts of the other two variants (Chien *et al*., 2009).

Cajanus cajan

The hypoglycemic effect of biscuits produced from flour blends of three medicinal foods (*C. cajan* legume, *M. paradisica* fruit and *M. olifeira* seed) on streptozotocin-induced diabetic rats and fed with high-fat diet was evalued. After 14 days of fed, it was observed that the formulated biscuits from the flour blends reduced the activities of pancreas α-amylase and intestinal α-glucosidase compared with acarbose-treated diabetic rats (Sodipo *et al*., 2020).

The potential of a beverage prepared from *C. cajan* legume for lowering glucose and total cholesterol plasma levels in Alloxan-induced diabetic-hypercholesterolemia rats was studied. A doses of 2.7 g/kg of beverage reduced plasma glucose levels by 17.16% and 33.86% after 1 week and 2 week of intervention period respectively (Ariviani *et al*., 2018).

The anti-hyperglycemic effect of ethanolic extract of *C. cajan* leaves in oral glucose tolerance test with glucose-loaded mormoglycemic mice was evaluated. Doses of 400 and 800 mg/kg of extract caused a reduction by 50.03% and 45.94% respectively on blood glucose levels 2.5 hours after the administration, while the standard drug glimepiride (16.77 µg/kg) produced a 63.76% reduction (Manzo & Vitor, 2017).

The antidiabetic potential of the methanolic extract of *C. cajan* roots was evaluated in alloxan-induced diabetic and in oral glucose loaded mice. The result show that the extract at doses of 200 and 400 mg/kg the reduction in blood glucose levels were 37.17 and 54.51%, respectively, while that reference drug metformin (50 mg/kg) reduced blood glucose levels by 65.81%. Equally, treatment with the extract (200 and 400 mg/kg) on oral glucose tolerance also significantly suppressed the rise in blood glucose level at 30 min by 137.39% and 171.19% respectively compared with control (Nahar *et al*., 2014).

The antidiabetic activity of methanol extract of *C. cajan* leaves was studied in alloxan-diabetic and in oral glucose loaded rats. The results showed that the extract at doses 400 and 600 mg/kg significantly reduced fasting blood sugar of alloxan diabetic rats at 6 hours by 67.7% and 71.3%, this last result was the same for glibenclamide (0.5 mg/kg). Likewise, treatment with the extract (400 and 600 mg/kg) on oral glucose tolerance also significantly suppressed the rise in blood glucose level at 60 min by 101.79% and 57.40% respectively compared with control (Ezike *et al*., 2010).

Cecropia obtusifolia

The aqueous extract from *C. obtusifolia* possesses an interesting pharmacological effect on type 2 diabetics. Herrera-Arellano *et al.* (2004) evaluated the clinical effect produced by the aqueous extract from *C. obtusifolia* leaves on type 2 non-controlled diabetes mellitus. All patients evaluated maintained their medical treatment and also received a prepared infusion of the dry leaves of the plant treatment for 21 days. The fasting blood glucose values were reduced by 15.25%, while cholesterol and triglycerides were decreased by 14.62% and 42.0%, respectively. A minimum percentage of patients (13.6%) showed slight side effects such as salivary flow, exhaustion and pyrosis.

In another study, Revilla-Monsalve *et al*. (2007) evaluated the hypoglycemic effect of aqueous extract of *C. obtusifolia* leaves in diagnosed type 2 diabetic patients. A daily dose of the aqueous extract was administered. The results proved a significant and sustained hypoglycemic effect of aqueous extract, reducing glucose levels by 17.24%, after 32 weeks of the daily administration of extract. The patients' reduced concentrations of glucose were maintained during the entire treatment and for an additional 4 weeks after suspending treatment. The treatment adherence was of 100%, and no adverse effects were reported.

The hypoglycemic effect of *C. obtusifolia* and *C. peralta* leaves in healthy mice and its correlation with the chlorogenic acid content was evaluated. Oral doses of 1 g/kg of methanol extracts of the two species showed a decrease in plasma glucose levels by 35.7% and 45.6% respectively, after 4 h of treatment. Likewise, both species showed concentration of 13.1 and 19.84 mg of chlorogenic acid per gram dry leaves, respectively. Proving that the hypoglycemic effect is correlated with the chlorogenic acid concentrations in plant leaves (Nicasio *et al*., 2005).

The hypoglycemic effects of aqueous and butanolic extracts of *C. obtusifolia* leaves in streptozotocin induced diabetic rats was evaluated. The both extracts showed their maximum effect at 3 h. Oral administration of aqueous extract at doses of 90 and 150 mg/kg showed reduction on plasma glucose concentration of 15.08% and 16.56%, respectively. The butanol extract at doses of 9 and 15 mg/kg reduced a 16.13% and 25.66%, respectively. In addition, also evaluated the hypoglycemic effects at 3 h of chlorogenic acid and isoorientin, compounds isolated from both extracts, which at dose of 10 mg/kg produced a significant decrease on plasma glucose levels of 25.66% and 27.06%, respectively. The two compounds had a better effect than glibenclamide (21.22%) (Andrade-Cetto & Wiedenfeld, 2001).

Citrus maxima

The antidiabetic effects of *C. maxima* peel on alloxan-induced diabetic adult male Wistar rats was investigated. Oral administration for 14 days of peel ethanolic extract at doses of 200 mg, 400 mg, and 600 mg/kg body weight decreased significantly blood glucose levels by 62.05%, 70.17% and 63.73% respectively, while the diabetic control group increased by 41.76% (Ani & Ochu, 2020).

The effect of *C. maxima* fruit peel supplementation in alloxan-induced diabetic rats was evaluated. *C. maxima* fruit peel supplementation (0.5% supplement with 100 g crushed food) for 21 days significantly reverted the glucose intolerance and liver enzymes activities to near normal levels. Moreover, *C. maxima* fruit peel supplementation prevented oxidative stress in liver of alloxan-induced diabetic rats. Also alloxan administration in rats caused inflammatory cells' infiltration and fibrosis in the liver which is ameliorated by *C. maxima* fruit peel supplementation (Ulla *et al*., 2019).

The effect of *C. maxima* juice on fasting blood glucose of alloxan-induced diabetic adult Wistar rats was investigated. Oral administration for 14 days of fruit juice at doses of 300 and 600 mg/kg decreased significantly blood glucose levels by 67.2% and 47.8% respectively, while the diabetic control group increased by 81.2% (Ani & Aginam, 2018).

Antidiabetic activity of several extract and dried juice of the fruits of *Citrus maxima* in alloxan-diabetic rats was evaluated. For a dose of 200 mg/kg, the ethyl acetate, ethanolic extract, and dried juice showed a decrease in blood glucose levels for an acute study (24 h) by 38.78%, 32.29% and 38.71%, respectively. But none of the extract showed significant results in prolonged study (Bhandurge *et al*., 2010).

The anti-hyperglycemic activity of methanol extract of *Citrus maxima* leaves in streptozotocin-induced diabetic rats. Oral administration for 15 days of extract at doses of 200 and 400 mg/kg produced a reduction in blood glucose levels of 68% and 76%, respectively (KunduSen *et al*., 2011).

Coffea arabica

The antidiabetic potential of *C. arabica* pulp using an experimental model of type 2 diabetes in rats induced by a high-fat diet and a single low dose of streptozotocin was evaluated. Oral administration of pulp aqueous extract at a dose of 1000 mg/Kg body weight for 12 weeks, decreases plasma glucose by 44.58%, when compared to control animals. While the standard anti-hyperglycemic drug metformin (30 mg/kg) decreases plasma glucose by 49.01% (Boonphang *et al*., 2021).

The antidiabetic effect of *C. arabica* was evaluated in alloxan-induced diabetic rats. The aqueous extract of coffee green grain at doses of 63 and 93 mg/kg was administered once daily for fifteen days. After of treatment, aqueous extract of coffee green grain significantly decreased blood glucose levels by 83% and 84% respectively, while that the standard drug glyburide (0.36 mg/kg) produced a 74% reduction (Campos-Florian *et al*., 2013).

The effect of a tincture (hydroethanolic extract) of roasted and ground coffee on plasma levels glucose in alloxan-induced diabetic rats was studied. After 30 days of treatment, oral administration of doses of 1.0 and 2.0 ml of the coffee tincture reduced the concentrations of glucose by 20% and 24% respectively. The tincture was prepared by mixing 30 g of roasted and ground coffee (variety Catuaí Vermelho) diluted in 100 ml of water/ethanol (70:30) (Cardoso *et al*., 2011).

Cymbopogon citratus

The antidiabetic effects of citral isolated of *C. citratus* leaves on streptozotocin induced diabetic dyslipidemic rats was studied. An oral administration of citral at a dose of 45 mg/kg for 28 days decreased the blood glucose levels and significantly increased level of insulin as similar to glibenclamide treatment (600 µg/kg) when compared to the diabetes control group (Mishra *et al*., 2019).

The antidiabetic activity of the organic and non-organic cultivation of *C. citratus* leaves in streptozotocin-induced diabetic rats was evaluated. At the dose of 200 mg/kg, after 21 days of treatment, the organic plant aqueous extract exhibited a better antidiabetic activity than non-organic plant aqueous extract, both reducing blood glucose levels by 43.44% and 29.16%, respectively; while glibenclamide as positive control (10 mg/kg) caused a decreased of 58.56% (Itankar *et al*., 2019).

The antidiabetic activity of several extracts of *C. citratus* leaves using *in vitro* α-amylase and α-glucosidase activity was evaluated. The methanol extract showed a better α-amylase inhibitory activity (EC_{50} = 0.29 mg/ml) than acarbose (EC_{50} = 0.56 mg/ml). The hexane and ethyl acetate extracts showed very high inhibitory activity (99%) at 1 mg/ml against the α-glucosidase enzyme (Boaduo *et al*., 2014).

The hypoglycemic potential of aqueous extract of *C. citratus* leaves on alloxan-induced diabetic rats was studied. A treatment daily with a dose at 1.5 ml/100 g body weight of extract for 4 weeks showed as result a decrease blood glucose levels of 26.60% (Ewenighi *et al*., 2013).

The antidiabetic activity of essential oils of stalks and leaves of *C. citratus* using *in vitro* β-glucosidase inhibition assay. The essential oil extracted from stalk had highest inhibition with up to 89.63% at the ratio of 1:2 for the volume concentration of essential oil per volume of solvent. While the essential oil extracted from leaves obtained an inhibition activity at 79.26% against β-glucosidase enzyme at the same ratio value of 1:2 (Mirghani *et al*., 2012).

The hypoglycemic effect of aqueous extract of *C. citratus* leaves in normal rats for 42 days was investigated. For a dose at 500 mg/kg the results showed an approximate decrease of 25% on the fasting plasma glucose levels when compared to control (Adeneye & Agbaje, 2007).

Eryngium foetidum

The antidiabetic potential of various extracts of *E. foetidum* leaves using *in vitro* α-amylase activity was evaluated. The methanolic, ethanolic and aqueous extracts showed an inhibition percentage against α-amylase enzyme of 46.02%, 52.20% and 30.12%, respectively (Malik *et al*., 2016).

Euterpe oleracea

The effect of the hydroalcoholic extract of *E. oleracea* seed associated with exercise training on diabetic complications induced by high-fat diet plus streptozotocin in rats was evaluated. The extract (200 mg/kg/day) was administered by gavage and the exercise training was performed on a treadmill (30 min/day; 5 days/week) for 4 weeks after the diabetes induction. The treatment with the extract reduced blood glucose, but the association of the extract plus exercise training had a better effect (de Bem *et al*., 2018).

Gomphrena globosa

The hypoglycemic effect of ethanolic extract of *G. globosa* leaves in alloxan induced diabetic rats was studied. Administration of the extract at a dose of 200 mg/kg and 100 mg/kg for 4 days showed a significant reduction in the blood glucose level by 46.92% and 45.54% respectively, while anti-hyperglycemic agent diabenese (100 mg/kg) reduced blood glucose levels by 53.45% (Omodamiro & Jimoh, 2014).

Guazuma ulmifolia

The effect of oral administration of herbarium mixture of *G. ulmifolia and Tecoma stans* on metabolic profile in pacient with type 2 diabetes mellitus (T2DM) was evaluated. A randomized, double-blind, placebocontrolled, clinical trial was carried out in 40 patients. The administration of herbarium mixture (*G. ulmifolia*/ *T. stans*), 400 mg before each meal or placebo for 90 days in patients that were randomly assigned, improved the glycemic profile in patients with T2DM (Pascoe-González *et al*., 2020).

The antidiabetic activity of aqueous extract of *G. ulmifolia* leaves and its combination with ethanolic extract of the powdered grains of *Curcuma xanthorrhiza* in alloxan-induced diabetic mice was evaluated. A treatment during 28 days with a dose at 50 mg/kg of extract showed a reduction of plasma glucose level by 57.74%. The combination of extract of *G. ulmifolia* at dose of 50 mg/kg with *C. xanthorrhiza* at dose of 25 mg/kg showed a percentage of reduction with 61.62%, while that glibenclamide and metformin showed a reduction of plasma glucose level by 49.20% and 70.50%, respectively (Adnyana *et al*., 2013).

Lantana camara

The inhibitory activity of *L. camara* leaves against α-glucosidase and α-amylase was evaluated using enzymatic protocols. The ethanolic extract showed a moderate α-glucosidase inhibition activity (IC_{50} = 0.428 mg/mL) and a low inhibitory effect on α-amylase (Ávila-Reyes *et al.*, 2019).

The antidiabetic potential of aqueous extract and a new compound isolated (stearoyl glucoside of ursolic acid) from the leaves of *L. camara* in streptozotocin-induced diabetic rats was evaluated. The aqueous extract at doses of 250 and 500 mg/kg showed a decreased in blood glucose level by 62.8% and 65.54%, respectively after 21 days of treatment. Likewise, the compound isolated at a dose of 0.3 mg/kg showed a decreased in blood glucose level by

67.61%. While that the standard drug glimepiride (0.1 mg/kg) showed a decreased in blood glucose level by 71.84% (Kazmi *et al*., 2012).

The anti-hyperglicemic activity of the methanol extract of *L. camara* leaves in alloxan-induced diabetic rats was evaluated. Oral administration of extract at doses of 200 and 400 mg/kg showed significant reduction in the blood glucose concentration by 50.03% and 55.62% respectively, after 14 days of treatment. While the standard drug glibenclamide (5 mg/kg) showed a reduction of in the blood glucose concentration by 59.38% (Ganesh *et al*., 2010).

Momordica charantia

M. charantia is one of the plants that has been investigated thoroughly for the treatment of diabetes. In several reviews have been grouped and documented the hypoglycemic effects of the seed, fruit pulp, leaves and whole plant of this specie. The hypoglycemic effects and antidiabetic activity have been studied in cell culture, animal models and human studies. All this studies showed that the blood glucose levels were significantly reduced compared to controls. Some studies also claimed that the hypoglycemic effect is comparable with oral medications such as tolbutamide, chlorpropamide and glibenclamide (Peter *et al*., 2020; Salehi *et al*., 2019; Tan *et al*., 2016; Joseph & Jini, 2013; Kumar *et al*., 2010; Leung *et al*., 2009; Grover & Yadav, 2004).

For example, Mahmoud *et al*. (2017) studied the antidiabetic activity of *M. charantia* fruit juice on streptozotocin-induced type 2 diabetes mellitus in rats. Fruit juice was orally administered at dose of 10 mL/kg/day either as prophylaxis for 14 days before induction of diabetes then 21 days of treatment, or as treatment given for 21 days after induction of diabetes. The results showed a significant reduction of serum glucose level by 46.33% and 40.89% for prophylaxis and treatment, respectively.

Musa paradisiaca

Anti-hyperglycemic activity of *M. paradisiaca*-based diet in alloxan-induced diabetic mellitus rats was studied. Anti-hyperglycemic activity of a M. paradisiaca-based diet in alloxan-induced diabetic mellitus rats was studied. After of 4 weeks feeding period the fasting blood glucose levels were lower in the diabetic rats fed M. paradisiaca-based diet and metformin treated group when compared with diabetic control (Ajiboye *et al*., 2017b).

The effect of unripe *M. paradisiaca* (plantain) supplemented diet on serum blood glucose on alloxan induced-diabetic albino rats was investigated. The feeding of the diabetic rats with supplemented diet 30% for 21 days reduced serum blood glucose, 223.42 to 98.54 mg/dL (Uhegbu *et al*., 2016).

Myrciaria dubia

In vivo effects of chronic ingestion of raw extracts derived from camu-camu (*M. dubia* McVaugh) frozen pulp on plasma lipid profile and oxidative stress in streptozotocin-induced diabetic rats was evaluated. Oral administration of camu-camu raw extracts (1 and 3 g/kg body weight, for 30 days) significantly increased plasma antioxidant activity, reduced triacylglycerol and total cholesterol and lipid peroxidation in the plasma of streptozotocin-induced diabetic rats. However, no effect was observed on glucose metabolism of diabetic rats, probably due to the severity of this model (Gonçalves *et al*., 2014).

Fujita *et al.* (2015) evaluated the anti-hyperglycemic property of the freeze-dried powder and spray-dried powder from camu-camu using *in vitro* enzyme assay models. The results showed that compared to acarbose (IC_{50} = 150 µg/mL), all camu-camu powders were highly effective in inhibiting α-glucosidase (IC_{50} between 4.50-10.83 µg/mL). In the case of the inhibition α-amylase, all camu camu powders analyzed were less efficient than ascarbose (IC_{50} = 3.50 µg/mL). Previously similar results showed de Azevêdo *et al*. (2014), where all extracts dried powder exhibited strong *in vitro* α-glucosidase and moderate α-amylase inhibitory activity. In both studies conclude camu-camu shows antidiabetic properties and has potential as part of dietary strategies in the management of early stages of type 2 diabetes and associated complications.

Peperomia pellucida

Hypoglycemic activity of *P. pellucida* in alloxan-induced diabetic rats was evaluated. The acetate extract of the whole plant at a dose of 300 mg/kg body weight produced a reduction of blood glucose level of 68.44%, after 7 days of treatment (Sheikh *et al*., 2013). 8,9-dimethoxy ellagic acid compounds isolated from ethyl acetate fraction of *P. pellucida* leaves, exhibited 33.74% blood glucose lowering in glycemic model at dose of 100 mg/kg (Susilawati *et al*., 2017). So too, this species has been used as a dietary supplement in animal models, finding a very good antidiabetic effect (Hamzah *et al*., 2012).

Persea americana

The beneficial effects of 28 days treatment with aqueous, ethanolic, and methanolic leaf extract were investigated on glucose homeostasis in type 2 diabetis mellitus using Wistar rats and by means of biochemical markers and intestinal absorption test of D-glucose. The results displayed that all extracts (100 mg/kg/day) significantly decrease blood glucose at the 28th day of treatment with pronounced effect for methanolic extract. The last one was the most effective in preventing intestinal glucose uptake up to 60.90% in relation to metformin (Kouamé *et al*., 2019).

Lima *et al*. (2012) investigated the hypoglycaemic of the leaves of *P. americana* in streptozotocin-induced diabetes rats. After the first week of treatment, the hydroalcoholic extract at doses of 150 and 300 mg/kg/day, significantly reduced fasting glucose levels in about 33 and 56%, respectively, when compared to the control diabetic. At the end of the treatment (4 weeks), the reduction was of 60 and 71%, respectively, compared to the diabetic control. In another study, the effects of the seed of *P. americana* on alloxan induced diabetic rats was investigated. After 4 week of treatment, the aqueous extract at doses of 400, 800 and 1200 mg/kg body weight showed significant decrease in blood glucose level by 59.3, 35.7 and 72.9%, respectively (Alhassan *et al*., 2012).

Petiveria alliacea

The hypoglycemic activity of *P. alliacea* leaves was evaluated, contrary to other studies, the aqueous extract at doses of 200 and 400 mg/kg/day for a treatment of three weeks, caused no significant hypoglycemic effect in streptozotocin-induced diabetic rats, instead, blood glucose increased weekly throughout the experiment. These findings this could hold significant implications for its use in traditional medicine of *P. alliacea* as a hypoglycemic agent where it is used in an aqueous form (Christie & Levy, 2013).

Phyllanthus niruri

Antidiabetes activity of the combination of *P. niruri* and *Zingiber americans* using oral glucose tolerance and alloxan induced methods was evaluated. The results showed that the decrease of blood glucose levels on oral glucose tolerance method were 40.98, 44.84, and 47.02% at doses of 90, 135, and 203 mg/kg body weight, respectively compared to control. While the decrease in blood glucose levels in alloxan induced diabetic mice were 33.05, 38.82, and 41.79% at dose 90, 135, and 203 mg/kg BW, respectively compared to control (Elfahmi *et al*., 2020).

The antidiabetic potential of the aerial parts of *P. niruri* using assays for α-glucosidase was investigated. The aqueous and ethanolic extracts showed α-glucosidase inhibitory activities with IC_{50} values of 3.7 and 6.3 µg/mL, respectively; whereas acarbose showed an IC_{50} value of 596.4 µg/mL (Beidokhti *et al*., 2017).

The antidiabetic properties of the aerial parts of *P. niruri* via metabolomics approach in streptozotocin-induced diabetic rats was evaluated. The administration of 500 mg/kg body weight of ethanolic extract caused the metabolic disorders of obese diabetic rats to be improved towards the normal state, showing a significant reduction in blood glucose and improved other bio-chemical parameters (Mediani *et al*., 2016).

The antidiabetic effect of aerial parts of *P. niuri* was studied by evaluating the effect of its chronic administration on the blood glucose level of alloxan-induced diabetic rats. Daily oral administration of methanol extract at doses of 200 and 400 mg/kg for 28 days, showed reduction on blood glucose levels by 53.24% and 66.76%, respectively, while that glibenclamide showed a reduction of plasma glucose level by 62.48% (Okoli *et al*., 2010).

Phyllanthus urinaria

Trinh *et al*. (2016) evaluated the antidiabetic potential of the aerial parts of *P. urinaria* through their ability to inhibit α-glucosidase and α-amylase, two key enzymes involved in serum glucose regulation. The aqueous and ethanol extracts significantly inhibited α-glucosidase with IC_{50} of 14.6 and 39.7 µg/mL, respectively. In the α-amylase inhibition assay, the extract did not have a significant inhibitory effect. In another study, partitioning of the methanolic extract of *P. urinaria* using EtOAc extract demonstrated high inhibitory activity against porcine pancreatic amylase (Gunawan-puteri *et al*., 2012).

Physalis angulata

The antidiabetic activity of *P. angulata* leaves using an in vitro model was investigated. The result showed that ethanol extract was able to inhibit α-amylase activity up to 56.6 ± 4.7% at the concentration of 200 µg/mL (Nguyen & Vo, 2020).

In a study carry out by Adewoye *et al*.

(2016), oral treatment for 14 days with methanol extract of *P. angulata* (whole plant), at dose of 500 mg/kg, showed significant decreased in blood glucose levels in alloxan-induced diabetic male rats, compared to diabetic untreated group rats.

Plantago major

P. major and other six Palestenian plants were tested to evaluate their α-amylase inhibition actvity trough their hydropholic and lipophilic fractions. Lipophilic fractions exhibited superior performance to alfa amylase inhibitory activity with IC_{50} values of 70.72, 25.34, 61.35 µg/mL for *S. irio*, *A. palaestinum* and *P. major* respectively (Hawash *et al*., 2019).

The beneficial effects of the aerial part of *P. major* on hyperglycemia-mediated oxidative stress and inflammatory responses alloxan induced diabetes mellitus rats was studied. Oral administration of methanol extract at dose of 500 mg/kg showed that the extract promotes glucose uptake in rats with efficient insulin secreting pancreas, exerting an antidiabetic activity by stimulating of insulin and producing a hypoglycemic effect (Abud *et al*., 2017).

Antidiabetic activity of *P. major* leaves using streptozotocin-induced diabetic rats was evaluated. The continuous post-treatment for 14 days wiht the alcoholic extract at dose of 1000 mg/kg showed significant fall in blood glucose level by 65% (Abdulghani *et al*., 2014).

Portulaca oleracea

A studied carried out by Park *et al*. (2019) investigated the inhibitory activity of 5,7 dimethoxy-3-(2'hydro-xybenzyl)-4-chromanone (5,7-D chromanone) isolated from *P. oleracea* L. on carbohydrate digesting enzymes and its capacity to improve postpandrial hyperglicemia in streptozotocyn-induced diabetic mice. 5,7-D chromanone strongly inhibited α-glucosidase and α-amylase (IC_{50} = 15.03 and 12.39 µM, respectively). The inhibitions were more effective than acarbose, which was the positive control. The increase in blood glucose level after ingesting starch was more significantly alleviated in the 5,7-D chromanone ingested group than in the control group of diabetic mice. In the control group, blood glucose levels were 24.64, 27.22, and 26.37 mM, and in the 5,7-D chromanone ingested group were 23.87, 23.38, and 21.42 mM at 30, 60, and 120 min, respectively.

The protective effect of the aerial part of *P. oleracea* against diabetes in alloxan-induced diabetic rats was studied. Rats were fed by gavage with *P. oleracea* extract aqueous daily (250 mg/kg) for 4 weeks and then receive daily ip injection of alloxan (at 75 mg/kg) for 5 days. Pre-treatment of the rats with the extract allowed that the level of glucose in blood did not rise much after induction with alloxan (125 mg/dL) compared to the rats that were not given the extract (293 mg/dL) (Ramadan *et al*., 2017).

Antidiabetic activity of *P. oleracea* seeds on subjects with type-2 diabetic was investigated, to provide scientific basis for clinical use. A daily dose of 10 g of seeds showed a decreased in post-prandial blood glucose level by 66.57% after 8 weeks of treatment. While that the standard drug Metformin (1500 mg/day) showed a decreased in post-prandial blood glucose level by 53.01% (El-Sayed, 2011).

Scoparia dulcis

A review published by Pamunuwa *et al*. (2016), discusses the antidiabetic activities of *S. dulcis* as well as its antioxidant and anti-inflammatory properties in relation to the diabetes and its complications. Scientific studies shows as to the antidiabetic effects of crude extracts of *S. dulcis*. The aqueous extract of the leaves of *S. dulcis* demonstrated hypoglycemic activity at doses of 200 and 450 mg/kg body weight for a treatment orally for 42 and 45 days on streptozotocin and alloxan induced diabetic rats, respectively (Pari & Venkateswaran, 2002; Latha & Pari, 2004).

The hypoglycemic effect of the aerial parts of *S. dulcis* in alloxan-induced diabetic mice was evaluated. Oral administration of ethanol extract at doses of 100 and 200 mg/kg for 2 weeks, showed reduction on blood glucose levels by 31.87% and 46.97%, respectively, when compared to control animals. While the standard anti-hyperglycemic drug metformin (600 µg/kg) showed a reduction on blood glucose level by 50.74% (Zulfiker *et al*., 2010).

The hypoglycemic activity of the aerial parts of *S. dulcis* in streptozotocin-induced diabetic rats was studied. The methanol extracts a dose of 200 and 400 mg/kg, after 21 days of treatment, showed significant inhibition of blood glucose level (33.4% and 44.9%, respectively) as compared to control and similar to that of standard glibenclamide (47.7%) (Mishra *et al*., 2013).

Otherwise, according to Coulibaly *et al*. (2020), the aqueous and acetone extract of aerial part of *S. dulcis* not showed any inhibitory activity in vitro againts α-amylase and α-glucosidase.

Senna reticulata

A preliminary study of the hypoglycemic effect of *S. reticulata* leaves in alloxan-induced diabetic rats was evaluated. Oral administration of aqueous extract at a dose of 1g/kg, presented a decrease in glycemia on days 7 and 15 by 6.25% compared to the initial values on day 0. Although there is a decrease in blood glucose, the extract not showed a significant hypo-glycemic effect (Cristancho *et al*., 2009).

Solanum sessiliflorum

The influence of *S. sessiliflorum* fruits fibres on the glucose concentration in streptozotocin-induced diabetic rats was evaluated. The rats feeding with fibre 10%, as part of its daily diet, presented a reduction on blood glucose level by 40.87% after 4 weeks (Yuyama *et al*., 2005).

Stachytarpheta cayennensis

The hypoglycemic activity of *S. cayennensis* leaf in alloxan-induced diabetic rats was studied. Oral administration of aqueous (125 mg/kg) and methanol (2000 mg/kg) extracts showed significant blood glucose reductions by 43% and 53%, respectively, at the end of 4 h, similar to the strong effect of glibenclamide (5 mg/kg) (Adebajo *et al*., 2007).

Syzygium cumini

The antidiabetic effect of hydro-ethanolic seed extract of *S. cumini* on an established model of diabetes mellitus with a combination of streptozotocin and high fat diet (over 12 weeks) in adult male Wistar albino rats was evaluated. Daily oral administration of extract at doses of 100 and 200 mg/Kg for 21 days, showed reduction on blood glucose levels of 170.83 and 210.17 mg/dl, respectively (Asanaliyar & Nadig, 2021).

Different parts of *S. cumini* especially fruits, seeds and stem bark have been extensively studied as an alternative treatment of diabetes (Srivastava & Chandra, 2013; Ayyanar *et al*., 2013).

The hypoglycemic effect of *S. cumini* seed powder was studied on fasting blood glucose levels in alloxan-induced diabetic rats. Three different doses, 0.25, 0.5 and 0.75 g/kg of ethanolic extract administered orally resulted in 10-33, 33–52 and 40–82% decreases in blood glucose level on days 8, 15 and 30 respectively (Singh & Gupta, 2007).

The potential of seed and fruit extracts of *S. cumini* against hyperglycemia were evaluated. Fruit and seed's ethanolic extracts based diets were provided to normal rats and high sucrose diet induced diabetic rats for sixty days. Fruit extract attenuated serum glucose levels to 5.35% and 12.29% in normal and hyperglycemic rats, respectively; while insulin levels were improved by 2.82% and 6.19%, correspondingly. Whereas, seed extract reduced glucose to 7.04% and 14.36% and showed 3.56% and 7.24% higher insulin levels in normal and hyperglycemic rats, respectively (Raza *et al*., 2017).

Terminalia catappa

The antidiabetic activity of ethanolic extract of *T. catappa* L. leaves on streptozotocin-induced diabetic mice was evaluated. After 14 days of treatment, the dose of 100 mg/kg was more optimal in lowering blood glucose level (Hayaza *et al*., 2019).

The antidiabetic effect of *T. catappa* leaves on streptozotocin-treated rats was evaluated. Daily oral administration of ethanolic extract at doses of 300 and 500 mg/kg for 45 days, reduced blood glucose levels and other diabetes-related parameters and increased insulin levels (Divya *et al*., 2019).

The antidiabetic effect of various extract of *T. catappa* fruits on fasting blood sugar levels in alloxan-induced diabetic rats were investigated. After three weeks of daily treatment, methanolic and aqueous extracts at dose levels 1/5 of their lethal dose led to a dose-dependent fall in blood sugar levels by 60% approximately (Nagappa *et al*., 2003).

Uncaria tomentosa

The immuno-modulatory potential of *U. tomentosa* stem bark on the progression of immune-mediated diabetes induced by multiple low-doses of streptozotocin rats was investigated. The hydroethanol extract reduced the glycemic level and delay the diabetes incidence. A treatment for 21 days with a concentration of 400 mg/kg of extract exhibited high inhibition of diabetes incidence by 15% (Domingues *et al*., 2011).

DISCUSSION

The review describes the scientific production of the anti-diabetes potential of Amazonian plants during the period of 2001-2021.

Different reviews about the antidiabetic potential of medicinal plants have been published around the world, where more than 800 plant species having hypoglycemic activity are reported in literature, there being coincidences with our study regarding some medicinal plants widely used as antidiabetics that grow in different geographical areas, such is the case of *Momordica charantia* and

Anacardium occidentale (Giovannini *et al*., 2016). Medicinal plants with insignificant toxicity and no side effects are notable therapeutic options for the treatment of diabetes (Herrera-Añazco *et al*., 2019).

Streptozotocin and alloxan were the chemical agents most used in diabetes models induced, substances capable of selectively destroying the β cells of the pancreas. Both drugs exert their diabetogenic action when they are administered parenterally: intravenously, intraperitoneally or subcutaneously. The dose of these agents required for inducing diabetes depends on the animal species, route of administration and nutritional status (Fröde & Medeiros, 2008).

Although there are other *in vitro* methods such as the determination of glycosylated hemoglobin, the α-amylase and α-glucosidase inhibition techniques are the ones that are reported the most since, apparently, they are the ones with the best results and the ones with the greatest accessibility (Papoutsis *et al*., 2021).

Most reviewed studies report the amount of reduction of blood glucose that is always evaluated after a period of fasting following acute or chronic treatment, the comparative studies are carried out mostly with nondiabetic and/or diabetic animal groups treated with known antidiabetic drugs, but results do not permit to further explore the mechanism of action of the studied plant species. Generally, anti-hyperglycemic effects of plants are attributed to their ability to restore the function of pancreatic tissues by causing an increase in insulin output or inhibit the intestinal absorption of glucose or to the facilitation of metabolites in insulin dependent processes (Kimani *et al*., 2015). In another cases, the hypoglycemic effect of a plant implicates a dual action, promoting insulin secretion, liver glycogen accumulation, and hepatoprotection by decreasing collagen fibers and inflammatory markers, whereas it improves lipid metabolism (Fortis-Barrera *et al*., 2020). In some species some adverse reactions have been found, this may be perhaps due to the geographic location or the collection or study area of the plants, that could be a promotor of production of other different bioactive compounds. Likewise, there is a variation in the effective dose according to the origin of the species. From the studies of anti-diabetes activity reported in this review, no studies have been carried out with species collected in the Peruvian Amazon previously.

CONCLUSIONS

This review is a quick reference of the antidiabetic potential of medicinal plants from the Peruvian Amazon to the scientific community and public looking for sources of knowledge of medicinal plants for treatment of diabetes. The antidiabetic potential reported for the species were shown by the whole plant, a specific part of the plant, or a particular extract. Nearly 77 species have been identified used by Amazonian inhabitants in the treatment of this pathology, from those 46.75% of species presented hypoglycemic activity. It is evidenced that traditional knowledge is a truthful source for the search of potentially useful antidiabetic drugs, proving the value of traditional knowledge that guides the way to scientific investigations. It is necessary to carry out studies of the hypoglycemic activity of the traditionally used species in the Peruvian Amazon for the treatment of diabetes to compare their activity with their peers from other geographical origins. The Amazonian promising species in which reports of the antidiabetic effects were not found could be an alternative for future research.

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