Chapter 15

# Medicinal Plants for the Treatment of Diabetes

María Cristina Revilla Monsalve[1]*, Myriam Marlenn Altamirano Bustamante[1], Ana Gabriela Gallardo Hernández[1], Noemí Grisel Castillo González and Elsa Verónica de la Chesnaye Caraveo[1]

[1]Medical Research Unit in Metabolic Diseases, UMAE, Hospital de Cardiología, Centro Médico Nacional Siglo XXI, México
*Corresponding author: cristina_revilla@hotmail.com

**ABSTRACT**

Diabetes is a complex and multifactorial disease that affects the metabolic pathways of carbohydrates, proteins, and lipids. Chronic high blood glucose levels, a result of altered insulin secretion and/or insulin resistance, is the main characteristic of this disease that affects the function of multiple organs, deteriorates the patient´s quality of life, and finally causes death. In its development and progression, the interaction of genetic and environmental factors plays a very important role. In 2021, 537 million adults between 20-79 years old had diabetes. Despite the arsenal of medications and treatments, according to estimates, this number will increase to 643 million in 2030 and 783 million by 2045. This increase is associated with late diagnosis, lack of treatment adherence, the high costs of medications, and unhealthy lifestyles. In recent years, much scientific research has been done to demonstrate the hypoglycemic properties of many plants and the reduced side effects, so that the use of medicinal plants is gaining strength, as a safe alternative that can contribute to the control of this disease.

**KEYWORDS**
Diabetes, Hypoglycemic effect, Secondary metabolites, Medicinal plants.

Received: 18-May-2024
Revised: 12-July-2024
Accepted: 13-August-2024

A Publication of Unique Scientific Publishers

**Cite this Article as:** Revilla MMC, Altamirano BMM, Gallardo HAG, Castillo GNG and de la Chesnaye CEV, 2024. Medicinal plants for the treatment of diabetes. In: Abbas RZ, Khan AMA, Qamar W, Arshad J and Mehnaz S (eds), Complementary and Alternative Medicine: Botanicals/Homeopathy/Herbal Medicine. Unique Scientific Publishers, Faisalabad, Pakistan, pp: 133-142. https://doi.org/10.47278/book.CAM/2024.097

## INTRODUCTION

Disease has accompanied human beings since their origins and obviously increased when humans settled down and started living in groups. To survive, humanity had to find healing alternatives and so, the use of medicinal plants was one of their options. Initially, the use of the different plants was in a "trial and error" manner, but with time the "healers" were able to identify the benefits of the different plants, or parts of the plants, that had healing properties and their adequate usage to combat the different diseases (Eknoyan and Nagy, 2005). We must point out that in ancient times, disease was associated with the punishment of gods, and the participation of demons, and so the treatment required breaking the enchantments and curses and prayers to the gods, and in some cultures this relationship still exists.

Although archeologists are finding evidence of the presence of some diseases in the skeletons of humans of various cultures, we don´t have reliable information related to the presence of different diseases that affected humans before the appearance of the first writing system, due to the knowledge was only orally transmitted and, the information may not be accurate. Writing systems appeared more or less at the same time in Mesopotamia and Egypt in 3000 BC. The first reports of the presence and treatments of different diseases and especially of diabetes can be found in the Ebers papyrus (1500 BC) where a description of symptoms related to diabetes, like excessive thirst, and copious urination that was treated with plant extracts, can be found. In India (500 BC), the Samhita document describes diabetes based on its symptoms such as the sweet taste of urine, its sticky sensation, and its ability to attract ants, associating this disease with excessive consumption of foods, especially sweets. In ancient China (475 BC), they also considered classic symptoms such as polyuria, polydipsia, polyphagia, and weight loss and was defined as wasting-thirst (xiao-ke) (King and Rubin, 2003; Loriaux, 2006).

In the 2nd century AD, Aretaeus of Cappadocia introduced the term diabetes, its origin is the Greek verb *διαβαινω* (diabaino) which means siphon because the liquid does not remain in the body and runs out. In his work, he mentioned that the kidneys and bladder never stopped producing water and made a broad and detailed description of this condition. Curiously, he pointed out that "this disease is not very common in men". For treatment, he recommended the consumption of cereals, milk and wine, the topical application of poultices and the administration of the miraculous remedy "*Theriac*" composed of 70 ingredients including minerals, herbs, poisons and animal meat, combined with honey, which with modifications has been used for more than two millennia (Laios et al., 2012).

**Diabetes as a Multifactorial Disease**

Diabetes is one of the diseases that humanity has historically faced. It is a multifactorial and complex disease that affects the metabolic pathways of carbohydrates, proteins, and lipids and is mainly characterized by chronic high glucose levels, a consequence of altered insulin secretion and/or insulin resistance (Deepthi et al., 2018). This chronic hyperglycemia alters the function of multiple organs, progressively deteriorates the quality of life, and finally causes death with a high economic and social cost for the family and health systems. The interaction of genetic and environmental factors plays a very important role in the development and progression of this disease. Ethnicity, family history of diabetes, previous gestational diabetes, older age, overweight and obesity, unhealthy diet habits, sedentary lifestyle, and smoking are risk factors that increase the probability of developing diabetes and in consequence, the chronic complications that are characteristic of this disease and responsible for the high morbidity and mortality related to this condition (ADA, 2023).

The complications that affect patients to different degrees are of two type macro and microvascular. The latter are more prevalent and include neuropathy, nephropathy, and retinopathy. Cardiovascular disease, stroke, and peripheral artery disease are the macrovascular complications that affect these patients. A special complication is the diabetic foot syndrome, which is associated with neuropathy, peripheral artery disease, and infection and is responsible for the high frequency of amputations. Gum disease and alterations in the ability to resist infections are complications that affect the quality of life of diabetic patients (Ali and Ahmed, 2021; Tomic et al., 2022).

The American Diabetes Association (ADA) has classified this disease into the following categories:

1. Type 1 diabetes (T1D) caused by autoimmune destruction of β cells, usually leading to absolute insulin deficiency, including latent autoimmune diabetes in adulthood.
2. Type 2 diabetes (T2D) has a multifactorial origin, characterized by a progressive loss of adequate insulin secretion, or by increased resistance to it.
3. Other specific types of diabetes are due to other causes, such as illness or the use of medications. Among the first is the monogenic diabetes syndrome, which includes neonatal diabetes and juvenile diabetes with onset in maturity. Exocrine diseases of the pancreas, such as cystic neoplasms, neuroendocrine tumors, pancreatitis, pancreatic insufficiency, or cystic fibrosis. On the other hand, induced diabetes caused by the prolonged consumption of drugs or chemical substances. This consumption may be associated with diseases or specialized surgical procedures, such as glucocorticoids, used in the treatment of HIV/AIDS, or medications administered after an organ transplant.
4. Gestational diabetes mellitus (GDM, diagnosed in the second or third trimester of pregnancy, and that was not clearly overt diabetes before pregnancy.

Each of the different types of diabetes has specific characteristics and treatment requirements; therefore, its identification using established diagnostic criteria is of utmost importance and can contribute to personalized and more effective management. (ADA, 2023).

**Global Dimensions of Diabetes**

Diabetes is a highly prevalent disease, affecting all age groups. According to the IDF (International Diabetes Federation) report published in 2021, 537 million adults (20-79 years) live with diabetes (1 in 10), estimating that this number will increase to 643 million in 2030 and 783 million in 2045 (IDF, 2021). Table 1 compiles the data recorded for this disease in 2021, by modality.

**Table 1:** Global prevalence of diabetes by regions (2021)

| REGION | T2D (> 19 years) | Undiagnosed proportion (%) | T1D (0-14 years) | T1D (0-19 years) | Gestational Diabetes (GDM) (%) |
|---|---|---|---|---|---|
| Africa | 23,633,900 | 53.6 | 26,300 | 59,500 | 13 |
| Europe | 61,425,100 | 35.7 | 162,600 | 294,900 | 15 |
| Middle East and North Africa | 72,671,900 | 37.6 | 108,900 | 192,500 | 14.1 |
| North America and Caribbean | 50,547,000 | 24.2 | 98,200 | 192,500 | 20.7 |
| South and Central America | 32,497,100 | 32.8 | 64,600 | 121,300 | 15.8 |
| South-East Asia | 90,204,500 | 51.3 | 132,200 | 244,500 | 25.9 |
| Western Pacific | 205,640,200 | 52.8 | 58,900 | 107,900 | 14 |
| Average | 76,659,957 | 41.1 | 93,100 | 173,300 | 16.9 |

**Source:** Preparation with data reported by IDF (2021)

Although the most prevalent type of diabetes is T2D, the rest of the data is alarming. Based on average values, this means that 41.1% of the world's population suffering from diabetes is still undiagnosed, which would significantly increase the numbers in each region. Additionally, 16.9% of newborns developed in a hyperglycemic environment, a condition that is a risk factor for developing T2D, obesity, insulin resistance and other metabolic disorders in adulthood. Due to its distribution and prevalence, the largest number of adults with diabetes live in low- and middle-income countries. In 2021, diabetes was responsible for 6.7 million deaths. Health expenditures amounted to 966 billion dollars, increasing 315% in the last 15 years (IDF, 2021). Table 2 integrates the data by region comparing the most prevalent countries.

At the regional level, the highest number of cases corresponds to the Western Pacific and South East Asia, associated with the population of India and China, respectively. In terms of real impact, when comparing the prevalence with the total population by country, the highest percentage value corresponds to Pakistan with 14.25% of the population (1.4 out of 10) that has T2D, followed by Mexico (11.15%) and Turkey (10.72%) (World Bank, 2021; IDF, 2021).

**Table 2:** Prevalence of cases and deaths associated with diabetes by region. Most prevalent countries (2021)

| Region | Cases | Deaths | Country | Prevalence (Thousands) | Population (Millions) | With diabetes (%) |
|---|---|---|---|---|---|---|
| Africa | 23,633,900 | 416,163 | South Africa | 4,234.0 | 59.4 | 7.13 |
| | | | Nigeria | 3,623.5 | 213.4 | 1.70 |
| | | | Tanzania | 2,884.0 | 63.6 | 4.54 |
| Europe | 61,425,100 | 1,111,201 | Turkey | 9,020.9 | 84.1 | 10.72 |
| | | | Russia | 7,392.1 | 144.1 | 5.13 |
| | | | Germany | 6,199.9 | 83.2 | 7.45 |
| Middle East and North Africa | 72,671,900 | 796,362 | Pakistan | 32,964.5 | 231.4 | 14.25 |
| | | | Egypt | 10,930.7 | 109.3 | 10.00 |
| | | | Iran | 5,450.3 | 87.9 | 6.20 |
| North America and Caribbean | 50,547,000 | 930,692 | United States | 32,215.3 | 332.0 | 9.70 |
| | | | Mexico | 14,123.2 | 126.7 | 11.15 |
| | | | Canada | 2,974.0 | 38.2 | 7.78 |
| South and Central America | 32,497,100 | 410,206 | Brazil | 15,733.6 | 214.3 | 7.34 |
| | | | Colombia | 3,443.6 | 51.5 | 6.68 |
| | | | Venezuela | 2,280.0 | 28.2 | 8.09 |
| South-East Asia | 90,204,500 | 747,367 | India | 74,194.7 | 1,407.6 | 5.27 |
| | | | Bangladesh | 13,136.3 | 169.4 | 7.76 |
| | | | Sri Lanka | 1,417.6 | 22.2 | 6.40 |
| Western Pacific | 205,640,200 | 2,281,732 | China | 140,869.6 | 1,412.4 | 9.97 |
| | | | Indonesia | 19,465.1 | 273.8 | 7.11 |
| | | | Japan | 1,005.0 | 125.7 | 0.80 |
| Total | 536,619,700 | 6,693,723 | | | | |

**Source:** Preparation with data reported by IDF (2021) and World Bank (2021)

These data allow us to understand the magnitude of the problem that diabetes represents. According to the Pan American Health Organization, prevalence is increasing most rapidly in low- and middle-income countries. This disease increases the risk of suffering from cardiovascular diseases, one of the main causes of strokes, heart attacks, and loss of limbs due to amputation (mainly due to the development of diabetic foot). These conditions place diabetes among the main causes of death and disability-adjusted life years (PAHO, 2021).

Despite knowledge about the risk factors associated with diabetes and the arsenal of hypoglycemic medications, different treatments, combinations of drug, and algorithms that have been proposed, reality shows that the progress made to control this disease is not very encouraging. Faced with this problem, some international agencies are proposing different strategies, like the ADA/EASD Precision Medicine in Diabetes Initiative (PMDI) (2018), and the Global Diabetes Pact, proposed by WHO (2021). (PAHO, 2021; Nolan et al., 2022).

Achieving the objectives of these initiatives will undoubtedly provide great benefits for the control and treatment of diabetes. While this happens, treatments based on hypoglycemic drugs, remain the conventional option. These include Sulfonylureas, Glinides or Metaglinides, Biguanides, Thiazolidinediones, α-glucosidase inhibitors, GLP-1 agonists and DPP-4 antagonists, mainly (Rodríguez-Rivera et al., 2017).

These drugs have different mechanisms of action, either by increasing insulin sensitivity, as a complement to insulin, by increasing insulin secretion levels, or by promoting glucose absorption. Although they manage to control blood glucose levels, they also induce adverse effects. Some of these effects include the development of hypothyroidism, tachycardia, liver failure and, lactic acidosis, among many others. In addition to this, the resistance that patients can develop to drugs, supports the search for other alternatives like the development of new drugs, where plants are the best option, due to the bioactive compounds they generate as part of their metabolism (Alam et al., 2022).

**Plant Metabolism and Bioactive Compounds**

From a physiological point of view, unlike the rest of living beings, plants are the only ones with a double metabolism. Secondary metabolism in plants is essential in the production of defensive agents that increase both their adaptation to changing environmental conditions, as well as their defense mechanisms against their predators. During this process, the plant carries out the biogenesis of different compounds, which have particular properties and specific mechanisms of action. They constitute the "natural compounds" that give plants their medicinal properties. The synthesis of these compounds occurs from the products generated in the primary metabolism processes of plants (Photosynthesis, Citric Acid Cycle, Glycolysis, Transamination and Amino acid synthesis, among others). For example, a product of glycolysis is Acetyl-

CoA, which is the precursor of acetogenins, terpenes, and steroids. While propanoids, flavonoids and alkaloids come from products of photosynthesis (Rungsung et al., 2015; Chomel et al., 2016; Deepa et al., 2018).

Due to their chemical composition, the functions that these bioactive compounds fulfill in plants are diverse. This composition is what also gives medicinal properties to the plants. Table 3 presents a comparison in this regard, considering exclusively the medicinal properties associated with diabetes.

**Table 3:** Function of some active compounds in plants and medicinal properties in diabetes

| Compound | Functions in the plant | Medicinal properties against DM | Source |
|---|---|---|---|
| Alkaloids | Nitrogen storage. Defense against predators (bitter taste and toxic properties for animals). | Increased glucose uptake. | Chomel et al. (2016); Ríos et al. (2016) |
| Phenolic acids | Allelopathy (influence on growth and development). Decreases decomposition time. Protection of DNA and lipids of the cell membrane. | Prevent oxidative damage Reduce metabolic alterations associated with TD2 (increased circulating glucose, lower insulin secretion) | Chomel et al. (2016), Cereceres-Aragón et al. (2019) |
| Flavonoids | They define the aroma and pigments of plants. Function as antioxidants, antifungal and antibacterial | Hypoglycemic agents Antihyperglycemics Antidiabetic | González-Sánchez et al. (2011), Chomel et al. (2016) |
| Tannins | Polyphenols most abundant in woody plants. They protect the plant against herbivores and pathogens. | Glycation inhibition Hypoglycemic effect Inhibition of tyrosine phosphatase (negative regulator of the insulin signaling pathway) | Chomel et al. (2016), Kumar et al. (2021) |
| Terpens | Confer resistance to the plant against biotic and abiotic stress | Inhibition of carbohydrate metabolism enzymes | Castro et al. (2014), Chomel et al. (2016) |

**Source: Self-made**

Due to the medicinal properties associated with the bioactive compounds of plants, these compounds are incorporated in the preparation of more than 25% of current drugs. Many studies report that plants under abiotic stress – caused by adverse environmental conditions – activate the production of new compounds or increase the concentrations of those they already produce; to strengthen their adaptation mechanisms. These plants offer greater possibilities for therapeutic use. This characteristic is very important since the conditions in which the plants grow are fundamental. The differences in the effectiveness of treatments, as well as the diversity of plants used, largely depend on the places and conditions in which the plants grow (Yeshi et al., 2022).

**Approaches to the Study of the Therapeutic Properties of Active Plant Compounds**

Secondary metabolites represent an incalculable natural resource, due to their great abundance and diversity.
The development of cutting-edge techniques (such as mass spectrometry), through which greater and better characterization of these compounds is achieved, supports this consideration. However, it is also pertinent to consider that, despite the progress made, in many cases, a limitation for the study of the effects and properties of these compounds is the yields obtained. Despite this, the number of investigations carried out to verify the therapeutic effects increases progressively.

The selection of plant species is not arbitrary, as it depends on the background and objectives of the research, as well as the availability and access to the plants in question. With all this, the differentiation of the properties of each plant allows us to go from generalization to deepening, by characterizing the attributes of plants, and glimpse their possibilities as a complementary alternative in the control or treatment of different diseases (Li et al., 2020).

As part of the knowledge currently available, there is certainty that the identification of different biosynthetic routes gives secondary metabolites different chemical characteristics, and therefore, different properties as therapeutic agents. Identifying three groups of a) Nitrogen compounds, which include alkaloids, glucosides, and cyanogenic glucosinolates; b) Phenolic compounds, such as flavonoids and phenylpropanoids; and c) Terpenes, which include carotenoids, glycosides, saponins and steroids (Fang et al., 2011; Yeshi et al., 2022).

Other factors that affect the medicinal potential of plants is the environmental conditions in which they develop. The concentration of nutrients in the soil, temperature, and relative humidity, among other environmental factors, are determining factors. Likewise, the accumulation and distribution of secondary metabolites is variable from one plant to another, as well as between the components of the same plant. Assessments made in this regard show that the concentrations of metabolites are similar between roots (or rhizomes) and stem, but different from the leaves, and these with respect to the flowers, fruits, and seeds, in which they are very similar. In general, the leaves have the highest content of metabolites, which is why they are widely used in the studies carried out (Belheir et al., 2016; Borges et al., 2017).

**Medicinal Plants for Diabetes**

Diabetes is a rapidly and actively spreading disease, in which the number of cases increases constantly and significantly. Although it does not meet the requirement of being restricted to a certain geographic area, it is an epidemic. Its global distribution, although it brings it closer to a pandemic, being present on all continents, definitively distances it from this denotation, as it is a non-contagious or transmissible disease. This places diabetes between these two epidemiological notions (Kharroubi and Darwish 2015; Barba, 2018).

The above reflects the magnitude and complexity of this disease, as well as the impact it generates on the world. The problem tends to become more acute due to changes in social habits that have been setting a trend to increase calorie consumption and reduce energy expenditure due to the lack of physical activity. This, in addition to increasing the number of overweight and obese people, increases the chances of developing the disease, especially those who have a genetic predisposition. Part of the complexity is that a large percentage of people who suffer from diabetes remain undiagnosed. Of those diagnosed, a significant number do not follow their treatment adequately. The lack of access to medications, abandonment of treatment, inadequate diet, and lack of physical activity aggravates this problem and, promote the increase in the T2D complications. (Ginter and Simko, 2013; Heredia-Morales and Gallegos, 2022).

In addition, and no less important, is the fact that although there are different pharmacological options to treat diabetes, their effectiveness is being compromised, both due to resistance and the side effects caused by the treatments. An alternative that is gaining more strength is the use of medicinal plants that contribute to the care of this disease. Beyond recovering the popular herbal tradition, various studies carried out for just over half a century have demonstrated the effectiveness of the use of plants in diabetes care. Among other aspects, they show the effectiveness of increasing and improving insulin secretion, promoting the absorption of glucose by muscle and adipose tissues, as well as inhibiting both the absorption of glucose in the intestine and the production of glucose from liver cells and inflammatory activities (Li et al., 2013; Alam et al., 2022).

With the results of the research, it has been possible to know the secondary metabolites of different plants. Table 4 shows the bioactive compounds identified for different botanical species. Variations in the content of metabolites confer different properties to plants.

**Table 4:** Bioactive Compounds identified in some of the different medicinal plants with antidiabetic properties.

| Botanical Species | Bioactive Compounds | Source |
|---|---|---|
| *Ficus* spp. | Flavonoids | Deepa et al. (2018) |
| *F. benghalensis,* | Phenolic acids | |
| *F. carica* | Tannins | |
| *F. glomerata* | Alkaloids | |
| *F. glumosa* | Glycosides | |
| *F. racemosa* | Coumarins | |
| *F. religiosa* | Triterpenoids | |
| | Sterols | |
| | Vitamin E | |
| *Tecoma stans* | Alkaloids | Alonso et al. (2010) |
| | Triterpenes | |
| | Phenolic compounds | |
| *Costus pictus* | Phenolic acids | Sidhu et al., (2012) |
| | Flavonoids | |
| | Proanthocyanidins | |
| *Cistus laurifolius* | Favonoids | Orhan et al. (2013) |
| *Hunteria umbellate* | Alkaloids | Igbe et al. (2009) |
| | Flavonoids | |
| | Glycosides | |
| *Rehmania glutinosa* | Iridoids Monoterpenes Glycosides Phenols Flavonoid | Jeonga et al. (2013) |
| *Vaccimium arctostaphylos* | Anthocynins | Feshani et al. (2011) |
| *Amaranthus viridis* | Alkaloids Steroids Glycosides Saponins Tannins | Pandhare et al. (2012) |

**Source: Self-made**

Knowledge about secondary metabolites in plants makes it possible to carry out research to identify their mechanisms of action, in this case, for diabetes. Table 5 integrates some examples of research generated around diabetes. In general, each study´s results vary, depending on the used methodology. They can vary from the type of research (in vitro, in vivo, ex vivo, in silico, preclinical and clinical studies), extraction methods, and plant parts, among others. The common point is the evaluation of the medicinal properties of plants, as an alternative for the treatment of diabetes.

**Table 5:** Studies that exemplify the assessment of the effectiveness of medicinal plants in the treatment of diabetes

| Location | Characteristics and Results of the study | Source |
|---|---|---|
| Bosnia y Herzegovina | *in vitro* study<br>Objective: Determination of the polyphenolic composition and anti-diabetic activity<br>Measurement of anti-diabetic activity: % inhibition of α-amylase and α-glucosidase<br>Leaves of 5 plants for traditional use against DM:<br>*Agrimonia eupatoria*: 94% flavonoids. Activity: Excellent (the best)<br>*Salvia officinalis*: 60% flavonoids, 40% phenolic acids. Activity: Weak<br>*Trifolium pratense*: 45% flavonoids, 55% phenolic acids. Activity: Excellent<br>*Cichoriuma intybus*: 52% flavonoids, 48% phenolic acids. Activity: Moderate<br>*Vica minor*: 20% flavonoids, 80% phenolic acids. Activity: The weakest | Kukavica et al. (2024) |
| Mexico | *In vitro* study<br>Objective: Test the inhibitory activity of α-glucosidase in butanolic extracts of four Mexican plants and effect on plasma glucose (PG) levels.<br>*Cecropia obtusifolia*: Greater reduction in PG. IC (50) 14μ/ml.<br>*Equisetum myiochaetum*: No effect on PG. IC (50) No effect.<br>*Acosmium panamense*: Significant decrease in PG. IC(50) 109 μ/ml.<br>*Malmea depressa*: Significant decrease in PG. IC (50) 21 μ/ml | Andrade-Cetto and Heinrich (2005) |
| Paraguay | Clinical study<br>Objective: Description of medicinal plants and phytotherapeutics used against T2D.<br>63.4% of patients consume medicinal plants and phytotherapeutics for T2D.<br>Use of 23 different medicinal plants<br>Most consumed plants: *Jungia floribunda* (52%), *Artemisia absinthium* (40%), *Moringa oleifera* (36%) and *Cissus verticillata* (28%).<br>Average plant consumption/patient: 3<br>Most consumed portion: Leaves (90.8%)<br>Frequency of use: Daily<br>Average use time: 64 months | Acosta-Recalde et al. (2018) |
| South Africa | *In vitro* study<br>Objective: Evaluation of antidiabetic activity of plants used locally against T2D<br>Evaluation of antidiabetic activity: α-amylase and α-glucosidase activity and excretory activity of the islets of Langerhans<br>In extracts with hexane:<br>*Cymbopogon citratus*: α-amylase inhibition 34.99%<br>*Cucurbita pepo*: α-amylase inhibition 72.29%<br>*Hypoxis hemerocallidae*: Inhibition of α-amylase 54.0%<br>*Cinnamomum cassia*: α-amylase inhibition 99.93%<br>*Senna alexandrina*: Inhibition of α-amylase 97.10% | Boaduo et al. (2014) |
| Turkey | Experimental study<br>Objective: To evaluate the hypoglycemic effects of aqueous (AE) and ethanolic (EE) extracts of Cistus laurifolius<br>Effect evaluation: Inhibition of α-amylase and α-glucosidase enzymes<br>Normal rats (Control)<br>Glucose-loaded hyperglycemic rats: Weak hypoglycemic effect (11-20%)<br>Diabetic rats induced with stretozocin (STZ): Decrease in blood glucose levels (EE)<br>EEs were better inhibitors than AEs | Orhan et al. (2013) |

**Source: Self-made**

The results of these investigations make it possible to know the effects of each plant with medicinal properties. Table 6 shows some of these effects.

**Table 6:** Effects of different plant species associated with DM.

| Botanical Species | Effect | Source |
|---|---|---|
| *Acacia catechu* | Significant anti-hyperglycemic effect<br>Reduction in serum glucose levels<br>Inhibition of glucose absorption in the intestine | Rahmatullah et al. (2013) |
| *Ageratum conyzoides* | Reduction of blood glucose levels<br>Inhibition of hyperglycemia<br>Inhibition of α-glucosidase and α-amylase enzymes | Rafe (2017) |

| | | |
|---|---|---|
| *Aloe vera* | Reduction of blood glucose levels<br>Improves insulin secretion<br>Improves glucose metabolism | Unuofin and Lebelo (2020) |
| *Anacardium occidentale* | Antidiabetic activity<br>Hypoglycemic activity | Vargas-Arana et al. (2023) |
| *Andrographis paniculata* | Inhibition of hyperglycemia<br>Inhibition of α-glucosidase and α-amylase enzymes<br>Antidiabetic activity | Rafe (2017) |
| *Anoectochilus roxburgii* | Reduction of blood glucose levels<br>Improvements in the body's antioxidant capacity<br>Modulation of enzymes that metabolize glucose | Ye et al. (2017) |
| *Berberis aristata* | Regulation of glucose homeostasis<br>Reduced gluconeogenesis<br>Reduction of oxidative stress<br>Strong antihyperglycemic activity | Potdar et al. (2012) |
| *Cajanus cajan* | Hypoglycemic effect<br>Anti-hyperglycemic effect<br>Antidiabetic activity | Vargas-Arana et al. (2023) |
| *Cinnamomum verum* | Suppression of α-glucosidase and α-amylase activity<br>Improvements in postprandial blood glucose | Beejmohun et al. (2014) |
| *Dendrobium chrysotoxum* | Decreases the activation of retinal microglia (in diabetic retinopathy) | Ojha et al. (2017) |
| *Momordica charantia* | Inhibition of insulin degradation<br>Hyperglycemic activity | de Menezes et al. (2023) |
| *Panax ginseng* | Reduction of blood glucose levels<br>Decreased β-cell function<br>Decreased insulin resistance | Unuofin and Lebelo (2020) |
| *Portulaca oleracea* | Inhibition of α-glucosidase and α-amylase enzymes<br>Anti-hyperglycemic activity<br>Antidiabetic activity | Vargas-Arana et al. (2023) |
| *Salvia officinalis* | Significant reduction in blood glucose levels (humans) | Behradmanesh et al. (2013) |
| *Tecoma stans* | Stimulate the uptake of 2-NBDG by insulin-sensitive adipocytes<br>Antidiabetic effect | Alonso et al. (2010) |
| *Terminalia arjuna* | Hypoglycemic effect<br>Antidiabetic activity | Rafe (2017) |
| *Trifolium pratense* | Reduction of glycated hemoglobin<br>Reduction of hyperglycemia<br>Improvement in insulin sensitivity<br>Improvement in liver glycogen levels | Alam et al. (2022) |

**Source: Self-made**

**Conclusion**

The challenges to control the progressive increase in people suffering from diabetes are multivariate and it is necessary to demonstrate the benefits provided by the active compounds produced by plants. The use of medicinal plants, in addition to contributing to the development of new drugs, gives us the possibility of providing accessible treatments, ideally free of unwanted side or adverse effects to treat not only diabetes but also the associated complications at a much lower cost, affordable to patients. Much research is needed to demonstrate the effects of the plant extracts not only in animal models but also in humans by increasing the number of clinical double-blind placebo-controlled trails and very important the absence of adverse effects.

We have to keep in mind that natural products are not synonymous with non-toxic and safe. For this reason, scientific research is required to support ethnobotanical and ethnopharmacological knowledge.

## REFERENCES

Acosta-Recalde, P., Lugo, G., Vera, Z., Morinigo, M., Maidana, G.M. and Samaniego, L. (2018). Uso de plantas medicinales y fitoterápicos en pacientes con Diabetes Mellitus tipo 2. *Memorias del Instituto de Investigaciones en Ciencias de la Salud, 16*(2), 6-11. https://doi.org/10.18004/mem.iics/1812-9528/2018.016(02)06-011

ADA (2023). Diagnosis and Classification of Diabetes Mellitus. American Diabetes Association. *Diabetes Care 46*(Supplement 1), S19-S40 https://doi.org/10.2337/dc23-S002

Alam, S., Sarker, M.M.R., Sultana, T. N., Chowdhury, M.N.R., Rashid, M. A., Chaity, N. I., Zhao, C., Xiao, J., Hafez, E. E., Khan, S.A. and Mohamed, I. N. (2022). Antidiabetic Phytochemicals from Medicinal Plants: Prospective Candidates for New Drug Discovery and Development. *Frontiers in Endocrinology* (Lausanne), *13*: 800714. http://doi.org/ 10.3389/fendo.2022.800714. P

Ali, M. S. and Ahmed, A. B. (2021). Complication of Diabetes Mellitus. *Annals of the Romanian Society for Cell Biology*, *25*(3), 1546-1556. https://annalsofrscb.ro/index.php/journal/ article/view/1601/1343

Alonso, C. A. J., Zapata, B. R., Romo, Y. J., Camarillo-Ledesma, P., Gómez, S. M., Salazar, O. L. A. (2010). The antidiabetic plants *Tecoma stans* (L.) Juss. ex Kunth (Bignoniaceae) and *Teucrium cubense* Jacq (Lamiaceae) induce the incorporation of glucose in insulin-sensitive and insulin-resistant murine and human adipocytes. *Journal of Ethnopharmacology, 127*(1), 1-6. https://doi.org/10.1016/j.jep.2009.09.060

Andrade-Cetto, A. and Heinrich, M. (2005). Mexican plants with hypoglycaemic effect used in the treatment of diabetes. *Journal of Ethnopharmacology, 99*(3), 325-348. https://doi.org/10.1016/j.jep.2005.04.019

Barba, E. J. R. (2018). Diabetes: ¿Epidemia o pandemia? *Revista Latinoamericana de Patología Clínica y Medicina de Laboratorio, 65*(4), 211-221. https://www.medigraphic.com/pdfs/patol/pt-2018/pt184e.pdf

Beejmohun, V., Peytavy-Izard, M., Mignon, C., Muscente-Paque, D., Deplanque, X., Ripoll, C., and Chapal, N. (2014). Acute effect of Ceylon cinnamon extract on postprandial glycemia: alpha-amylase inhibition, starch tolerance test in rats, and randomized crossover clinical trial in healthy volunteers. *BMC Complementary Medicine and Therapies, 14:* 351. https://doi.org/10.1186/1472-6882-14-351

Behradmanesh, S., Derees, F. and Rafieian-kopaei, M. (2013). Effect of *Salvia officinalis* on diabetic patients. *Journal of Renal Injury Prevention, 2*(2), 51-51. https://doi.org/ 10.12861/jrip.2013.18

Belheir, A. S., Gaid, M., Liu, B., Hänsch, R. and Beerhues, L. (2016). Benzophenone synthase and chalcone synthase accumulate in the mesophyll of *Hypericum perforatum* leaves at different developmental stages. *Frontiers in Plant Science, 7,* 921. doi: http://doi.org/10.3389/fpls.2016.00921

Boaduo, N. K., Katerere, D., Eloff, J. N. and Naidoo, V. (2014). Evaluation of six plant species used traditionally in the treatment and control of diabetes mellitus in South Africa using in vitro methods. *Pharmaceutical Biology, 52*(6):756-61. https://doi.org/10.3109/13880209. 2013.869828

Borges, C. V., Minatel, I. O., Gomez-Gomez, H. A. and Lima, G. P. P. (2017). Medicinal Plants: Influence of Environmental Factors on the Content of Secondary Metabolites. In: Ghorbanpour, M., Varma, A. (Eds.) *Medicinal Plants and Environmental Challenges* (pp. 259-277). Springer International Publishing, Cham, Switzerland. https://doi.org/10.1007/978-3-319-68717-9_15

Castro, J.C.J. Villa, R.N. Ramirez, G.S.A., and Mosso, G.C. (2014). Medicinal use of antidiabetic plants in Oaxacan ethnobotanical tradition. *Revista Cubana de Plantas Medicinales*, *19*(1), 101-120. http://scielo.sld.cu/pdf/pla/v19n1/pla12114.pdf

Cereceres-Aragón, A., Rodrigo-García, J. Álvarez-Parrilla, E. and Rodríguez-Tadeo, A. (2019). Consumption of phenolic compounds in the elderly population. *Nutrición Hospitalaria, 36*(2), 470-478. https://dx.doi.org/10.20960/nh.2171

Chomel, M., Guittonny-Larchevêque, M., Fernandez, C., Gallet, C., DesRochers, A., Paré, D., Jackson, B. G. and Baldy, V. (2016). Plant secondary metabolites: a key driver of litter decomposition and soil nutrient cycling. *Journal of Ecology, 104*(6), 1527-1541. https://doi.org/10.1111/1365-2745.12644

Deepa, P., Sowndhararajan, K., Kim, S. and Park, S. J. (2018). A role of *Ficus* species in the management of diabetes mellitus: A review. *Journal of Ethnopharmacology*, *215*, 210-232. https://doi.org/10.1016/j.jep.2017.12.045

Deepthi, B., Sowjanya, K., Lidiya, B., Bhargavi, R. and Babu, P. (2018). A modern review of Diabetes Mellitus: An annihilatory metabolic disorder. *Journal ofIn Silico and In VitroPharmacology*o Pharmacol, 3(1), 14. http://doi.org/10.21767/2469-6692.100014

De Menezes, C.T., Souza, de A.E., Cavalcante, P.J. Coelho dos S.T. and Gomes de A.A.C. (2023). O uso do melão de são caetano (*Momordica charantia*) no tratamento de diabetes tipo 2: uma revisão sistemática da literatura. *Revista Foco 16*(12), e3860. http://doi.org/10.54751/revistafoco.v16n12-053

Eknoyan, G. and Nagy, J. (2005). A history of diabetes mellitus or how a disease of the kidneys evolved into a kidney disease. *Advances in Chronic Kidney Disease, 12*(2), 223-229. http://doi.org/10.1053/j.ackd.2005.01.002

Fang, X., Yang, C. Q., Wei, Y. K., Ma, Q. X. Yang, L. and Chen, X. Y. (2011). Genomics Grand for Diversified Plant Secondary Metabolites. *Plant Diversity, 33*(01), *53-64.* http://doi.org/10.3724/SP.J.1143.2011.10233

Feshani, A. M., Kouhsari, S. M. and Mohammadi, S. (2011). *Vaccinium arctostaphylos*, a common herbal medicine in Iran: molecular and biochemical study of its antidiabetic effects on alloxan-diabetic Wistar rats. *Journal of Ethnopharmacology, 133*(1), 67-74. http://doi.org/10.1016/j.jep.2010.09.002

Ginter, E., and Simko, V. (2013). Global Prevalence and Future of Diabetes Mellitus. In: Ahmad, S.I. (Eds) *Diabetes. Advances in Experimental Medicine and Biology*, vol 771 (pp. 35-41). Springer, New York, NY. https://doi.org/10.1007/978-1-4614-5441-0_5

González-Sánchez, A., Cabañas-Wuan, Á., Arana-Argáez, V., Hernández-Núñez, E. and Ortiz-Andrade, R. (2011). Citroflavonoids as an alternative for the treatment of diabetes and its complications. *Revista Mexicana de Ciencias Framacéuticas, 42*(3), 17-26. https://www.scielo.org.mx/pdf/rmcf/v42n3/v42n3a3.pdf

Heredia-Morales, M. and Gallegos, C. E. C. (2022). Risk of type 2 diabetes mellitus and its determinants. *Enfermería Global,* (65), 191-201. https://dx.doi.org/10.6018/eglobal.482971

IDF (2021). *IDF Diabetes Atlas*. 10th Edition. International Diabetes Federation. https://diabetesatlas.org/data/

Igbe, I., Omogbai, E. K. I. and Ozolua, R. I. (2009). Hypoglycemic activity of aqueous seed extract of Hunteria umbellate in normal and streptozotocin-induced diabetic rats. *Pharmaceutical Biology, 47*(10), 1011-1016. http://doi.org/10.1080/13880200902973803

Jeonga, H. J., Kimb, J. S., Hyunc, T. K., Yanga, J., Kangd, H. H., Chod, J. C., Yeomd, H. M. and Kim, M. J. (2013). *In vitro* antioxidant and antidiabetic activities of *Rehmannia glutinosa* tuberous root extracts. *Science Asia, 39*(6), 605-609. http://doi.org/ 10.2306/scienceasia1513-1874.2013.39.605

Kharroubi, A. T., and Darwish, H. M. (2015). Diabetes mellitus: The epidemic of the century. *World Journal of Diabetes, 6*(6), 850-867. https://dx.doi.org/10.4239/wjd.v6.i6.850

King, K. M. and Rubin, G. (2003). A history of diabetes: from antiquity to discovering insulin. *British Journal of Nursing, 12*(18), 1091-1095. http://doi.org/10.12968/ bjon.2003.12.18.11775

Kukavica, B., Škondrić, S., Trifković, T., Mišić, D., Gašić, U., Topalić-Trivunović, L., Savić, A., Velemir, A., Davidović-Plavšić, B., Šešić, M. and Lukić, N. (2024). Comparative polyphenolic profiling of five ethnomedicinal plants and their applicative potential in the treatment of type 2 diabetes. *Journal of Ethnopharmacology, 320,* 117377. https://doi.org/10.1016/j.jep.2023.117377

Kumar, M., Tomar, M., Amarowicz, R., Saurabh, V., Nair, M. S., Maheshwari, C., Sasi, M., Prajapati, U., Hasan, M., Singh, S., Changan, S., Prajapat, R.K., Berwal, M.K. and Satankar, V. (2021). Guava (*Psidium guajava* L.) Leaves: Nutritional Composition, Phytochemical Profile, and Health-Promoting Bioactivities. *Foods, 10*(4):752. http://doi.org/10.3390/foods10040752

Laios, K., Karamanou, M., Saridaki, Z. and Androutsos, G. (2012). Aretaeus of Cappadocia and the first description of diabetes. *Hormones (Athens), 11*(1), 109-113. http://doi.org/ 10.1007/BF03401545

Li, G. Q., Kam, A. Wong, K. H., Zhou, X., Omar, E. A. Alqahtani, A. Li, K. M., Razmovski-Naumovski, V. and Chan, K. (2013). Herbal Medicines for the Management of Diabetes. In: Ahmad, S.I. (Eds) *Diabetes. Advances in Experimental Medicine and Biology*, vol 771. (pp. 396-413). Springer, New York, NY. https://doi.org/10.1007/978-1-4614-5441-0_28

Li, Y., Kong, D., Fu, Y. Sussman, M.R. and Wu, H. (2020). The effect of developmental and environmental factors on secondary. *Plant Physiology and Biochemistry, 148,* 80-89. https://doi.org/10.1016/j.plaphy.2020.01.006

metabolites in medicinal plants

Loriaux, L. (2006). Diabetes and the Ebers Papyrus: 1552 B.C. *The Endocrinologfist, 16*(2), 55-56. http://doi.org/10.1097/01.ten.0000202534.83446.69

Nolan, J. J., Kahkoska, A. R., Semnani-Azad, Z., Hivert, M. F., Ji, L., Mohan, V., Eckel, R. H., Philipson, L. H., Rich, S. S., Gruber, C. and Franks, P. W. (2022). ADA/EASD Precision Medicine in Diabetes Initiative: An International Perspective and Future Vision for Precision Medicine in Diabetes. *Diabetes Care, 45*(2), 261-266. https://doi.org/10.2337/dc21-2216

Ojha, S., Balaji, V., Sadek, B. and Rajesh, M. (2017). Beneficial effects of phytochemicals in diabetic retinopat (Shy: experimental and clinical evidence. *European Review for Medical and Pharmacological Sciences, 21*(11), 2769-2783. https://www.europeanreview.org/article/ 12899

Orhan, N., Aslan, M., Süküroğlu, M. and Deliorman, O. D. (2013). *In vivo* and *in vitro* antidiabetic effect of *Cistus laurifolius* L. and detection of major phenolic compounds by UPLC-TOF-MS analysis. *Journal of Ethnopharmacology. 146*(3), 859-865. https://doi.org/10.1016/j.jep.2013.02.016

PAHO (2021). Diabetes. Pan American Health Organization. https://www.paho.org/en/topics/diabetes

Pandhare, R., Balakrishnan, S., Mohite, P. and Khanage, S. (2012). Antidiabetic and antihyperlipidaemic potential of *Amaranthus viridis* (L.) Merr., in streptozotocin induced diabetic rats. *Asian Pacific Journal of Tropical Disease, 2*. (Supplement 1), S180-S185. https://doi.org/10.1016/S2222-1808(12)60148-0

Potdar, D., Hirwani, R. R. and Dhulap, S. (2012). Phyto-chemical and pharmacological applications of *Berberis aristata*. *Fitoterapia, 83*(5), 817-830. https://doi.org/ 10.1016/j.fitote.2012.04.012

Rafe, R. (2017). A review of five traditionally used anti-diabetic plants of Bangladesh and their pharmacological activities. *Asian Pacific Journal of Tropical Medicine, 10*(19), 933-939. https://doi.org/10.1016/j.apjtm.2017.09.002

Rahmatullah, M., Hossain, M., Mahmud, A., Sultana, N., Rahman, S. M., Islam, M. R., Khatoon, M. S., Jahan, S. and Islam, F. (2013). Antihyperglycemic and Antinociceptive activity evaluation of 'Khoyer' prepared from boiling the Wood of *Acacia catechu* in water. *African Journal of Traditional, Complementary and Alternative Medicines: AJTCAM, 10*(4), 1-5. https://doi.org/10.4314/ajtcam.v10i4.1

Ríos, J. L., Schinella, G. R. and Francini, F. (2016). Productos naturales para el tratamiento de la diabetes (II). *Revista de Fitoterapia,* 16(2), 49-55. https://ri.conicet.gov.ar/handle/11336/48927

Rodríguez-Rivera, N. S., Cuautle-Rodríguez, P. and Molina-Guarneros, J. A. (2017). Hipoglucemiantes orales para el tratamiento de diabetes mellitus tipo 2: uso y regulación en México. *Revista Hospital Juárez de México, 84*(4), 203-211. https://www.medigraphic.com/pdfs/juarez/ju-2017/ ju174e.pdf

Rungsung, W., Kumar, R. K., Dutta, S., Kumar, D. A. and Hazra, J. (2015). Secondary metabolites of plants in drugs discovery. *World Journal of Pharmaceutical Research, 4*(7), 604-613. https://doi.org/10.3390/medicines6020066

Sidhu, A. K., Wani, S. J., Tamboli, P. S. and Patil, S. N. (2012). *In vitro* evaluation of anti-diabetic activity of leaf and callus extracts of *Costus pictus*. *International Journal of Science and Research*, *3*(6), 1622-1625. https://www.ijsr.net/archive/v3i6/MDIwMTQ1NDI=.pdf

Tomic, D., Shaw, J.E. and Magliano, D.J. (2022).The burden and risks of emerging complications of diabetes mellitus. *Nature Reviews Endocrinology, 18, 525-539.* https://doi.org/10.1038/s41574-022-00690-7

Unuofin, J. O. and Lebelo, S.L. (2020). Antioxidant Effects and Mechanisms of Medicinal Plants and Their Bioactive Compounds for the Prevention and Treatment of Type 2 Diabetes: An Updated Review. *Oxidative Medicine and Cellular Longevity,* 2020:1356893. https://doi.org/10.1155/2020/1356893

Vargas-Arana, G., Rengifo-Salgado, E. and Simirgio, M. J. (2023). Antidiabetic potential of medicinal plants from the Peruvian Amazon: A review. *Boletín Latinoamericano y del Caribe de Plantas Medicinales, 22*(3), 277-300. https://doi.org/10.37360/blacpma.23.22.3.21

World Bank (2021). *Data Bank*. Total population. https://data.worldbank.org/ indicator/SP.POP.TOTL

Ye, S., Shao, Q. and Zhang, A. (2017). *Anoectochilus roxburghii*: A Review of Its Phytochemistry, Pharmacology, and Clinical Applications. *Journal of Ethnopharmacology, 209,* 184–202. https://doi.org/10.1016/j.jep.2017.07.032

Yeshi, K., Crayn, D., Ritmejeryté, E. and Wangchuckuk (2022). Plant Secondary Metabolites Produced in Response to Abiotic Stresses Has Potential Application in Pharmaceutical Product Development. *Molecules, 27*(1), 313. https://doi.org/10.3390/molecules27010313