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Evidence of the hypoglycemic capacity of some plant products as alternative treatment for type 2 diabetes

Evidencias de la capacidad hipoglucemiante de algunos productos vegetales como tratamiento alternativo de diabetes mellitus tipo dos

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Abstract

Type 2 diabetes is a disease characterized by the chronic presence of high glucose levels in blood caused by a defect in the secretion of insulin or in the action of said hormone in the body which must be treated integrally with a multidisciplinary approach. The alternative treatment of this disease with plants and their derivatives is a common practice around the world, especially in Latin America. There are several clinical studies, in vivo or in vitro that focus on assessing the hypoglycemic capacity of various plant products used empirically by the population for years for the phytotherapeutic treatment of the disease, as well as the chemicals related to the mechanism of action that produces this hypoglycemic effect. The aim of this article is to briefly review the evidence of the hypoglycemic capacity of some plant products for the alternative treatment of type 2 diabetes.

Keywords:

Hypoglycaemic capacity, phytochemicals, phytotherapy, type 2 diabetes

Resumen:

La diabetes tipo dos es una enfermedad que se caracteriza por la presencia crónica de niveles elevados de glucemia provocado por un defecto en la secreción de insulina o en la acción de dicha hormona en el organismo la cual debe ser tratada integralmente con un enfoque multidisciplinario. El tratamiento alternativo de esta enfermedad con plantas y sus derivados es una práctica común alrededor del mundo, especialmente en América Latina; existen diversos estudios de tipo clínico, *in vivo* o *in vitro* que se enfocan en evaluar la capacidad hipoglucemiante de diversos productos vegetales utilizados empíricamente por la población durante años para el tratamiento fitoterapéutico de la enfermedad, así como los químicos relacionados con el mecanismo de acción que produce dicho efecto hipoglucemiante. El presente artículo tiene como objetivo hacer una breve reseña de las evidencias de la capacidad hipoglucemiante de algunos productos vegetales para el tratamiento alternativo de la diabetes mellitus tipo 2.

Palabras Clave:

Capacidad hipoglucemiante, fitoquímicos, fitoterapia, diabetes mellitus tipo 2

INTRODUCTION

Type 2 diabetes is defined as a group of metabolic disorders characterized by chronic increase in blood glucose levels caused by a defect in the insulin secretion or in the action in the body.[1] It is a condition with multiple risk factors such as advanced age, obesity, sedentary lifestyle, family history with diabetes and socioeconomic level among others; it is of chronic and complex evolution.[2,3]

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Currently, diabetes is classified according to its etiological and pathophysiological characteristics, the most used is the one established by the American Diabetes Association (ADA) which includes 4 categories[4] that are described in Table 1.

In 2012, according to the World Health Organization, 90% of cases were represented by type 2 diabetes and, in 2015, the International Diabetes Federation determined around the world there were 415 million people with diabetes; 5 million died this year from diabetes[5] in Mexico. According to the Halfway National Survey of Health and Nutrition (ENSANUT MC by its initials in Spanish) 2016, 9.4% of the population indicated having a previous medical diagnosis of diabetes, with women being the most affected group of the population with a prevalence of 10.3% compared to the male prevalence of 8.4%; the majority of diabetics were between 60 and 79 years old.[6]

Table 1. Diabetes mellitus classification.

DIABETES MELLITUS CLASIFICATION	
Type one diabetes	Destruction of beta cells leading to absolute insulin deficiency
Type 2 diabetes	Progressive defect in insulin secretion, associated with an increase in insulin resistance
Gestational diabetes	Diagnosed in the 2nd and 3rd trimesters of pregnancy
Other types (Diabetes MODY)	Genetic defects in the function of beta cells Genetic defects in the action of insulin Exocrine pancreas disease (cystic fibrosis) Induced by chemicals or medications

Source: *Own elaboration with information from Barquilla García, Brief Update on Diabetes for General Practitioners. Rev. Esp. Sanid. Penit. 2017; 19: 57-65.*

DIAGNOSTIC CRITERIA FOR DIABETES

Diagnosing the disease in a timely manner is important, controlling it as soon as possible will help reduce and prevent complications.[7]

The criteria used to establish a diagnosis of diabetes are the following:

• Hemoglobin glucose A1c fraction (HbA1c) > 6.5%

• Fasting plasma glucose 8 hours > 126mg/dl

• Plasmatic glucose two hours after applying a glucose tolerance test by previously administering an anhydrous glucose load of 75 g dissolved in water > 200mg/dl

• Occasional glucose > 200 mg/dl in patients with classic symptoms of hyperglycemia.[3]

If the clinical diagnosis is not clear, then it will be necessary to confirm the diagnosis with a second analysis, if both analyzes exceed the figures previously indicated, then diabetes can be diagnosed; however, in case the results are incongruent, the test, whose results were altered, must be repeated.[3]

Patients affected by this condition have symptoms such as unusual thirst, extreme hunger, constant need to urinate, unusual weight loss, extreme fatigue and irritability, as well as frequent infections, blurred vision, wounds that take time to heal, tingling or numbness of hands and feet and recurrent infections in skin, gums and bladder; although sometimes people with type 2 diabetes are asymptomatic.[5]

PHARMACOLOGICAL CONTROL OF TYPE 2 DIABETES

The treatment of diabetes should be comprehensive, adequate and safe[8]; therefore, it is necessary to assess and guarantee medical treatment, and at the same time as it should be complemented with a nutritional assessment and frequent medical check-ups with a multidisciplinary team to keep adequate control and avoid the complications associated with the disease.[7]

With respect to the pharmacological treatment for type 2 diabetes, the Official Mexican Standard NOM-015-SSA2-2010 for the prevention, treatment and control of diabetes mellitus in primary care establishes that the treatment of choice for patients with type 2 diabetes are sulfonylureas, biguanides, insulins or combinations thereof.[9] Metformin is established as the first-line medical treatment unless there is a contraindication to its use, in which case the use of sulfonylureas is suggested, according to the guidelines for the treatment of type 2 diabetes.[10]

Due to the natural history of the disease, insulin is indicated at a specific time of diabetes mellitus type 2. For this, there must be the presence of several hyperglycemia, weight loss, elevated blood glucose levels despite combined oral treatment, decompensation due to ketoacidosis or hyperosmolar state, infections with hyperglycemia, pregnancy, glucocorticoid therapy, use of markers as a predictor of a high probability of insulin need.[11]

PLANT PRODUCTS WITH HYPOGLYCEMIC CAPACITY

Opuntia spp

The cactus *(Opuntia spp.)* belongs to the cacti. They grow wild in the American continent, primarily in Mexico. There

are 10 of the 258 existing species of the genus.[12] The consumption of its stems, fruits and flowers precedes from the prehispanic time[13], being Mexico the main producer and biggest consumer of this vegetable worldwide.[14] Its nutraceutical properties are of interest for the European and Asian markets, it is an excellent source of vitamins (C and E), minerals and soluble and insoluble fiber, as well as being beneficial in the natural treatment of various conditions[13] such as hypercholesterolemia, osteoporosis and diabetes.[12]

Hypoglycemic capacity of *Opuntia spp*.

Different studies suggest that both the fruit, the stem and the root in the different cactus species have hypoglycemic capacities. A study carried out in Hidalgo, Mexico by Fabella-Illescas et al (2015), where the effect of a fresh drink based on the cactus fruit was evaluated (*Nopalea cochenillifera*), on glucose levels, hemoglobin glucose, body weight, waist circumference and blood pressure in subjects with type 2 diabetes, hypertension, overweight and obesity to which they were administered daily, orally, for 3 days a drink prepared with 50 g of prickly pear in 250 ml of drinking water which was only liquefied keeping all the properties and fibers of the mentioned fruit. In this study it was found that the values for body weight, waist circumference, systolic and diastolic pressure showed significant differences at some point of the supplementation; in the glucose case, decreases are shown, however these were not statistically significant; regarding hemoglobin glucose, a statistically significant difference was found at 30 days after treatment.[15]

Another study comparing the hypoglycaemic activity of three natural products, among them the nopal root, of which two extracts were prepared in solutions with solvents of different polarities (water and ethanol) using a matter / solvent ratio of 1:20, a photochemical analysis was carried out that contemplates the detection of secondary metabolites generally related to biological activities. It was found that the possible mechanism of action of hypoglycaemic activity is due to the phenolic compounds contained in the natural products evaluated, in the case of chayote root, a greater number of flavonoids, carbohydrates, saponins and sterols in the phenolic extract; regarding the hypoglycaemic activity compared to the acarbose, the nopal root showed greater activity with both extracts, mostly with the aqueous one.[16]

STEVIA *(Stevia rabaudiana)*

Perennial herbaceous plant belonging to the Asteraceae family (Figure 1) is native from South America, it grows in tropical regions in a wild way, mainly in Paraguay and Argentina, although it has been cultivated for its sweetening properties for some decades.[17]

The compounds that give stevia the potential to sweeten up to 30 times more than conventional sugar[17] are known as steviol glucosides; which make up 15% of total composition. Stevioside, steviolbioside, rebaudioside A, B, C, D, E, F and dulcoside have been isolated and identified. The content of these phytochemicals varies according to the species and the culture conditions.[18]

The most studied steviol glucoside is stevioside; which is an extract with an aspect of whitish powder that crystallized since 1931, presents different beneficial uses to health, does not provide calories and has the ability to be antacid, cardiotonic and has hypoglycemic effect.[19]

Hypoglycemic evidence of the stevia genus

In 1986, Curi et al, studied the effect of an aqueous extract of Stevia leaves on glucose tolerance of 16 healthy volunteers, this extract was administered regularly for 3 days at 6 hour intervals, measuring tolerance to glucose before and after administration; the results of this study report an increase in glucose tolerance as well as a significant decrease in plasma glucose levels during the study and after the overnight fast in all participants.[20]

Figure 1. *Stevia rebaudiana* plant

Suanarunsawat et al, in 2004, conducted in vivo study where the glycemic effect of *Stevia rebaudiana* was evaluated by means of an aqueous extract and stevioside in a model of rats with diabetes induced by streptozocin, in which an experiment was carried out with six groups (3 groups with healthy rats and 3 groups with rats with induced diabetes) which were fed daily by intragastric intubation with water, stevioside (0.25 g/kg body weight) or aqueous extract of Stevia rebaudiana (4.66 g/Kg) for 8 weeks, which were treated with the same procedure. The plasma glucose level was determined once a week after an overnight fast and it was found that healthy rats fed with steviol showed a slight but significant increase with respect to plasma glucose after the third week. In the case of rats with induced diabetes there were no significant changes to report during the experiment. In the case of groups fed with *Stevia rebaudiana* it was found that plasma glucose did not present changes in healthy rats

but was significantly reduced in the second week until the end of the experiment in rats with induced diabetes.[21]

Ferreira et al., conducted a study whose objective was to compare the effect of an oral treatment with Stevia rebaudiana and steviosides on glycemia and gluconeogenesis in an in vivo test in male rats, in which they found that a dose of 5.5 mg extract from the dried leaves of *S. rebaudiana* per kg of weight administered for 15 days does not produce any effect, but if the dose increases to 20 mg/kg of body weight the plasma glucose concentration decreases when the activities of pyruvate carbolxilasa and phosphoenolpyruvate carboxykinase reduce. These results were observed in diabetic rats, since under normal conditions no effect was observed.[22]

CUCURBITACEAS FAMILY

The Cucurbitaceae family includes about 130 genera and more than 900 species. Table 2 shows a classification scheme that includes subfamilies, tribes, subtribes and genera popular of this family.[23] Within this family there are annual and perennial species; they are herbaceous plants of prostrate growth, better known as climbers.[24]

The species of this family plants are very important in the feeding of different regions in the world population, the most interesting cultivated species are watermelon, melon, cucumber, squash and chayote.[24]

The importance of this botanical family is not only in the field nutrition and its contributions, but also in the medicinal field[25]; the use of some of the fruits, foliages and roots of this family has been studied presenting various anti-inflammatory, antiviral and antibacterial properties[26], as well as finding in their content antioxidants to which hypoglycaemic capacity has been attributed.[16,25,26]

Table 2. Classification of cucurbits according to subfamilies, tribes and sub-tribes.

I. Sub family	**Zanonioideae**	
II. Sub family	**Cucurbitoideae**	
	Tribe 1	Melothrieae n=12
		Subtribe Melothriinae *Melothria, Zenheria, Cucumeropsis, Posadaea, Melancium, cucumis*
		Subtribe Dendrosicyoinae *Apodanthera, Kedrostis, Corallocarpus, Ibervillea*
		Subtribe Guraniinae *Gruania, Psiguria*
	Tribe 2	Schizopeponeae n=10 *Schizopepon*
	Tribe 3:	Joliflieae n=14,11,9 *Momordica, Phladiantha, Telfairia*
	Tribe 4	Trichosantheae n=11(12) Trichosanthes, Hodgsonia, Ampelosicyos
	Tribe 5	Benincaseae n=12(11,13,10) **Subtribe Benincasinae** *Coccinia, Benincasa, Lagenaria, Citrullus, Acanthosicyos, Praeciltrullus* **Subtribe Luffinae** *Luffa*
	Tribe 6	Cucurbiteae n=20 *Cucurbita, Sicana, Cayaponia*
	Tribe 7	Cyclambereae n=8 *Cyclanthera, Marah, Elaleriopsis, Rytidostylis*
	Tribe 8	Sicyoeae n=12 *Sechium, Sicyos*

Source: *Jeffrey C. A review of the cucurbitaceas. Bot. J. Linn Soc. 1980; 81(3):233-47.*

HIPOGLUCEMIATIVE CAPACITY OF THE CUCURBITACEA FAMILY

Root of wereke (*Ibervillae sonorae*)

Is a perennial dioecious plant that grows in vine shape, it gives small yel low flowers and round fruits that are green in its immature state and red with light stripes when it has matured[16]; the vegetative part of greater importance is the root which has a tuberculous appearance, of a large size similar to that of a jicama, is generally cultivated and distributed in the north of the country mainly in arid zones[27] which has been used by ethnic groups for the treatment of diseases such as arthritis, rheumatism, heart disease and diabetes.[28]

Hernández-Galicia et al (2007) attribute the hypoglycemic capacity of wereque to a group of monoglycerides and fatty acids that were isolated from the root of the plant by extraction with dichloromethane.[29]

Studies carried out with aqueous extracts of *Ibervillea sonorae* have shown that it reduces blood glucose in experimental animals; Table 3 gives a brief review of some of these experimental studies.[30-32]

Chilacayote (*Cucurbita ficifolia*)

Creeping-climbing plant native from South America belonging to genus pumpkins, is easy and rapid propagation and resistant to low temperatures; it gives a voluminous fruit that can reach up to 50 cm and weigh up to 15 kg.[33,34] The use in Mexican gastronomy is limited, since it is commonly used to make regional sweets or to feed livestock, due to the lack of knowledge regarding its chemical characteristics and its contribution to human consumption[35]. Muñoz et al, stressed that it is food rich in water, carbohydrates and its hypocaloric, with a varied content of minerals among which phosphorus (19 mg), calcium (15 mg), in addition to water-soluble vitamins such as vitamin C and niacin.[36] In addition to the afore mentioned, nutritional contributions, proteases have been isolated from the pulp of *C. ficifolia* [36] and compounds such as D-Quiro-Inositol that have therapeutic effects on diabetes.[34]

Ten patients diagnosed with type 2 diabetes and moderate hyperglycemia received a crude extract of *C. ficifolia* as part of a clinical trial conducted by Acosta-Patiño et al. (2001), which was administered as a single dose of 4 ml/kg of body weight, in two sessions with a difference of one week; these patients suspended taking their pharmacological treatment 24 hours prior to each intake as part of the study. It was found that the administration of said extract was followed by a significant decrease up to 5 hours after its administration.[37]

Alarcón-Aguilar (2002) studied the acute hypoglycemic effects of freeze-dried juice of chilacayote fruits in healthy mice and mice with alloxan-induced diabetes, which was administered intraperitoneally and orally. The one administered intraperitoneally caused, in a dose-dependent manner, a significant decrease in glycemia in healthy mice, and the one administered orally caused significant reductions in blood glucose levels of healthy mice, although the effect was less. In alloxan-diabetic mice, intraperitoneal administration showed an acute hypoglycaemic effect. In addition, the oral daily administration of lyophilized juice showed a significant reduction after 14 days of treatment.[38]

Bitter melon (*Momordica charantia*)

Annual vine, herbaceous, with yellow flowers, which gives a fruit with an elongated, tuberculated, orange-yellowish appearance as shown in Figure 2, with intense red seeds which owes its name to the bitter taste it has in all its parts[39,40], grows in the tropical areas of Asia, the Amazon, East Africa and the Caribbean.[41]

Among the photochemicals contained in *M. charantia* can be found glycosides, saponins, alkaloids, triterpenes, proteins and steroids[42], in its immature form, the fruit is a good source of vitamin C, in addition to providing vitamin A, phosphorus and iron.[40]

This plant has been used empirically as an anti-anemic, anti-inflammatory and healing[39], widely studied for its hypoglycemic effect[40] which is due to a mixture of saponins, peptides and alkaloids which are known as charantines.[42]

Muhammad (1982) conducted a study in which the whole fruit of pulverized *M. charantia* was tested in 8 patients with diabetes uncomplicated by age who were asked to consume the fruit in milk twice a day, in a dose of 50 mg/Kg. In addition, they were informed that they would continue with the diet deficient in carbohydrates and that they would not administer any other drug. The results obtained show that *M. charantia* produced a constant hypoglycemic effect in all study subjects without observing side effects.[43]

More recent studies have evaluated this benefit in combination with complications derived from diabetes, Abas et al, (2014) observed the effect of the extract of bitter melon on cardiac fibrosis induced by hyperglycemia in Sprague-Dawley rats with diabetes induced by streptozotocin. The group of interest was administered with 1.5 g/kg of body weight which after 28 days showed an increase in weight as well as a decrease in the level of glucose in blood, in addition to a significant increase in superoxide dismutase of cardiac tissues, the contents of glutathione and catalase; therefore it was concluded that *M. charantia* besides having hypoglycemic properties, is a cardioprotective and antioxidant.[44]

Figure 2. *Momordica charantia* fruit

Chayote (*Sechium edule*)

Table 3. Evidence of the hypoglycemic capacity of Ibervillae sonorae and its mechanism

Year	Author	Objective	Results	Study type	Reference
2002	Alarcón-Aguilar, et al.	To determine the acute effects of a lyophilized decoction of *I. sonorae* on the blood glucose levels of fasting mice	The extract significantly reduced the glycemia of mice with mild diabetes, not so with severe diabetes; so it is thought that the presence of insulin is necessary for the hypoglycemic activity.	In vivo	[30]
2011	Rivera-Ram F, et al.	To determine the effect of an aqueous extract of *I. sonorae* in a murine model of obesity and hyperglycemia	Simultaneous treatment of aqueous extract of *I. sonorae* in doses of 100, 200 and 400 mg / kg, decreased glucose and triglyceride levels, preventing an increase in body weight depending on the dose and decreasing hepatic lipid oxidation in a dose of 200 mg / kg	In vivo	[31]
2014	Zapata-Bustos R, et al.	Investigate the mechanism of the antidiabetic effect of an aqueous extract of *I. sonorae*.	The aqueous extract of *I. sonorae* stimulated the uptake of 2-NBDGlucose in cell cultures of mature human and murine adipocytes. In a dose of 50 mg / ml induced uptake of 2-NBDG EN 3T3-f442A, 3T3-L1 and insulin-sensitive adipocytes in 100%, 63% and 33%, compared with insulin control. In conclusion, *Ibervillea sonorae* exerts its antidiabetic properties through water soluble compounds that stimulate glucose uptake in human preadipocytes independent of PI3K and without proadipogenic effects.	In vitro	[32]

Climbing plant that belongs to the Cucurbitaceae family, is a species that was domesticated by the pre-Columbian cultures from Central America[45] although the most popular consumption is that of the fruit; the tender leaves and roots are also consumed as vegetables, and their gastronomic use is varied.[26]

It contains 90.8% of water, it contains carbohydrates (7.7%) as well as iron, calcium and phosphorus, this being the most abundant (30 mg).[45]

In addition to having hypotensive and anti-inflammatory capacity[46], it reduces the health risks associated with diabetes and obesity.[47,48] In a study conducted by Pérez-Ávila (2010) in which the hypoglycemic capacity of chayote juice was evaluated in Wistar rats with streptozotocin-induced diabetes, to which they were administered chayote juice diluted with drinking water in two presentations (filtered and unfiltered) finding that chayote juice diluted with unfiltered drinking water significantly decreased blood glucose concentration, in addition to presenting an increase in body weight of rats with diabetes, so the author suggests that such preparation may be a protective factor against diabetes.[49]

Siahaan et al, (2017) carried out a study in which the effect of an ethanolic extract of chayote was analyzed in order to decrease the level of blood sugar, using an animal model *(Mus musculus L*), in which it was found that there was a significant difference with respect to the control group.[50]

CONCLUSION

Diabetes represents a public health problem worldwide due to the high prevalence rates, which represent a serious health expense for the countries that suffer the most, which generally are developing countries. Natural medicine is a common practice in Latin American countries, a region of the world that also has a great diversity of plants that have hypoglycemic capacity. Many of these natural products used empirically have been studied. They present various photochemicals involved in hypoglycemic capacity, mainly antioxidants, which provide patients with diabetes a scientifically safe alternative for the treatment of their disease.

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