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ORIGINAL PAPERS

The Relevance of Some Plant Extracts In Human Patients and Animal Models of Diabetes

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Abstract. *Diabetes is a chronic disease characterized by hyperglycemia; medicinal plants have therapeutic uses in the management of diabetes. Various experiments have been conducted using animal models and clinical trials to explore the use of medicinal plants in the treatment of diabetes. The aim of this work is to present the relevance of some plant extracts in human patients and animal models of diabetes.*

Key words: Diabetes, Plant extract, Animal model, Clinical trial

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Introduction

Diabetes is a chronic disease characterized by a high level of glucose called hyperglycemia. It is due to a disorder in the secretion and/or action of the insulin secreted by the Beta-pancreatic cells. The main symptoms of hyperglycemia are polyuria, polydipsia, blurred vision, fatigue and involuntary weight loss [1]. According to the American Diabetes Association in 2019[2], diabetes is classified into 4 main types: type 1 diabetes, characterized by insufficient insulin production due to autoimmune destruction of pancreatic cells; type 2 diabetes, the most common form, is due to a deficiency in insulin secretion associated with poor use of insulin by the body; gestational diabetes results from an increase in blood sugar levels during pregnancy; and the fourth type is diabetes due to other causes such as monogenic diabetes syndrome (MODY), medication, etc.

Unbalanced diabetes leads to a risk of complications affecting various organs, and is the cause of significant morbidity and mortality worldwide. The complications of chronic diabetes are of two types: the first is microvascular includes neuropathy, nephropathy and retinopathy, while the second is macrovascular includes mainly cardiovascular disease, stroke and peripheral arterial disease (PAD) [3].

Diabetes and its complications are generally treated by diet and medical treatments (chemical, biochemical and pharmacological compounds). In the long term, drugs have harmful effects on the body's vital organs: the heart, liver, brain and kidneys. For this reason, alternative medicines are increasingly being used to treat diabetes and its complications, in particular the use of natural products derived from medicinal plants. Phytotherapy has long been a source of medicines, and the use of phytotherapy provides a valuable opportunity to discover new natural compounds with beneficial effects on glucose hemostasis and without side effects. Bioactive compounds present in plants (vegetable, Fruit, herb) include flavonoids, polyphenols, tannins, anthocyanins, alkaloids ... possess various pharmacological properties such as antidiabetic, antioxidant activity ... [4].

Animal model

Animals are widely used as models for the study of diabetes and its complications, and play an important role in understanding the genetic and functional characteristics of the disease.

Diabetes is induced experimentally in animals by chemical manipulations such as alloxan and streptozotocin, surgical such as pancreatectomy and genetic/immunological such as transgenic animals, of which chemical methods are the most widely used. Various models are used to study the different types of diabetes. Type 1 diabetes and gestational diabetes are generally induced by the injection of alloxan and streptozotocin, while the type 2 diabetes model is induced by alloxan, streptozotocin, streptozotocin + fat-fad, streptozotocin + fructose-fad and streptozotocin + nicotinamide. When using these chemicals several factors must be taken into consideration to induce hyperglycemia such as route of administration, sex, age of the animal, type of diabetes, dose... [5]. In addition to these methods mentioned above, immersion in a glucose solution is also a method used to induce diabetes [6].

Diabetic animals are used to study diabetogenic mechanisms and to search for new anti-diabetic drugs [7]. of which the natural one comes from herbs. Various studies have investigated the anti-diabetic effect of different plants in different animal models: rodents, rabbits, zebrafish, etc.

Rats: Studies show that the use of *Moringa Oliefera* extracts induces a reduction in glucose levels in diabetic rats, oral administration of 100 mg/kg of *Moringa Oliefera* extract in streptozotocin-induced hyperglycemic rats results in a reduction in blood glucose levels to a maximum of 54. 5% and an increase in

skeletal muscle glucose uptake to a maximum of 24.3%, also *M. Oliefera* shows an antioxidant effect that protects the pancreas against STZ-induced reactive oxygen species [8]. *Moringa Oliefera* extract corrects alloxan-induced hyperglycemia in diabetic albino rats and potentiates the antioxidant defense system by increasing antioxidant enzymes (SOD and CAT) and reducing lipid peroxidation, the effect of *Moringa Oliefera* on glycemic profit is also reflected in the cancellation of the gluconeogenesis pathway by reducing the expression of the mRNA of the pyruvate carboxylase enzyme and the improvement of the glycogenesis pathway by increasing the expression of the mRNA of the glycogen synthase enzyme in liver cells, it has a protective effect on the hepatocyte by reducing the expression of Caspase 3 mRNA, one of the main pathways of cell death being oxidative stress. In addition, *M. Oliefera* repairs liver and pancreatic cell architecture by restoring the degenerative effect of alloxan [9].

Curcumin is a principal pigment in *Curcuma Longa*, characterized by its hypocalcemia effect. It induces a drop in blood glucose, serum Total cholesterol, LDL, triglyceride and glycosylated hemoglobin levels respectively in diabetic rats, while HDL and plasma insulin levels rise, it also reduces renal damage and restores renal function by reducing serum creatine and urea levels. Administration of low-dose curcumin reduces lesions and preserves the cellular integrity of the liver, as shown by the reduction in liver enzyme levels (ALT, AST) [10] [11].

Diabetic cardiomyopathy is one of the complications of diabetes and is a consequence of alterations in myocardial function and structure. A dose of 100 mg/kg of curcumin causes a reduction in glucose levels and an increase in body weight in diabetic cardiomyopathy rats induced by a diet rich in glucose and fat, accompanied by an injection of STZ, thus improving cardiac function and structure, It also inhibits apoptosis by reducing the expression of caspase-3/cleaved caspase-3, Bax, gp91phox and Cyto C and an increase in the expression of Bcl-2, NQO1 and Nrf2 and via the Sirt1-Foxo1 and PI3K-Akt signaling pathways [12].

Mice: Studies show that intragastric administration of Sacha inchi extract *(Plukenetia volubilis L*) at a dose of 400 mg/kg results in a reduction in food consumption, correction of body weight loss, reduction in glycaemia and an improvement in glucose tolerance in diabetic mice. Sacha Inchi extracts also increased insulin sensitivity, reduced the pancreatic index and repaired pancreatic islet lesions. Sacha Inchi extract positively affects the richness and diversity of the intestinal microbiota and improves the taxonomic composition of the microbiota, with the elevation of numerous bacteria such as *Akkermansia, Parabacteroides* and *Muribaculum* and the reduction of others such as *Ruminiclostridium* and *Oscillibacter* [13].

Bouzghaya and *al* showed in 2020 that the aqueous extract of *Linum usitatissimum* seed caused a reduction in serum glucose in diabetic mice, an

improvement in glucose and insulin tolerance and corrected hepatic and renal oxidative stress induced by hyperglycemia by increasing antioxidant levels and reducing lipid peroxidation [14].

The work of Yan and *al* in 2016, on db/db transgenic mice, shows that mulberry anthocyanin extract has a protective effect against diabetes and this is reflected in its positive effect on the activation of the Akt pathway and the downstream pathway in the various organs (liver, muscle and adipocytes), resulting in an improvement in metabolic parameters, in particular a reduction in glucose, serum insulin, triglyceride, cholesterol and leptin levels and an increase in adiponectin levels [15].

Studies on mice with diabetic nephropathy, which is one of the complications of diabetes, induced by intraperitoneal injection of 240 mg/kg nicotinamide (NA) followed by injection of streptozotocin at a dose of 100 mg/kg with a high-fat diet show that *Myrciaria cauliflora* extract attenuates the effects of STZ/NA by lowering blood sugar levels, cholesterol and triglyceride levels, blood and urine nitrogen, blood creatinine and blood pressure. The extract also improves the ratio of urinary albumin to urinary creatinine, a sign of renal dysfunction. *Myrciaria cauliflora* extract also improves renal function and structure by reducing collagen and fibronectin deposition, thereby correcting glomerular atrophy and renal fibrosis and inhibiting activation of the Ras pathway. *Myrciaria cauliflora* extract also has antioxidant properties, reducing the generation of ROS and improving antioxidant defense. It also inhibits the renal inflammatory response by reducing the expression of inflammatory factors such as ICAM-1, VCAM-1, MCP-1, CSF-1, TNF-α, IL-1β and IL-6, reducing macrophage infiltration and inhibiting JAK, phosphorylated STAT3, PKC-β and NF-κB [16] [17].

Zebrafish: The work of Tomazi and *al* in 2021 shows that the latex extract of *Hancornia speciosa* Gomes has hypoglycemic properties, inducing a reduction in glycaemia in diabetic zebrafish induced by alloxan without any significant histological or biochemical changes [18].

Blood glucose, cholesterol and triglyceride levels were reduced in diabetic zebrafish induced by exposure to a 110 mM concentration of glucose following exposure to the extract of *Cinnamomum verum*, *Origanum majorana* and *Origanum vulgare*, while exposure to the polyherbs formed from these three extracts together induced a significant reduction in hyperglycemia and hyperlipidemia [19].

The increase in glycaemia caused by the injection of alloxan into zebrafish was reduced following the administration of 3g/kg of *Psychotria malayana* extract, proving its hypoglycemic property [20]. Similarly, according to Muñiz-Ramirez et al in 2021, treatment of zebrafish with methanolic extract of *Spondias purpurea* seeds reduces blood glucose and cholesterol levels, and inhibits the formation of advanced glycation end products in eye samples to a percentage of

98.5% for a dose of 90 mg/l, proving that its use can minimize diabetic complications [21].

Liquiritigenin, a flavonoid extracted from the roots of *Glycyrrhiza glabra*, has anti-hyperglycemic properties and prevents the development of diabetic complications, particularly those linked to bone metabolism, as demonstrated by Carnovali and *al* in 2019 following their study of zebra fish, they showed that liquiritigenin prevents the appearance of glycaemia after immersion in a glucose solution, in addition to inhibiting the production of advanced glycation end products and reducing parathormone levels, which has a positive effect on bone calcium metabolism. Liquiritigenin also regulates bone hemostasis by promoting osteoblast activity and inhibiting osteoclast activity. This is reflected in its ability to prevent the disappearance of alkaline phosphatase (ALP) activity and the increase in tartrate-resistant acid phosphatase (TRAP) activity, respectively [22].

Rabbit: The administration of butanolic and aqueous extracts of *Equisetum giganteum L* induced a decrease in glucose, triglyceride, cholesterol and glycosylated hemoglobin levels in alloxan-induced diabetic rabbits, and an increase in lipase activity was also observed, over time and in a dose-dependent manner. In addition, they protect the liver against steatosis, inflammatory infiltration and hyperemia [23].

The methanolic extract and oil of *Nigella sativa* are characterized by their hypoglycemic, hypolipidemic and antioxidant potential, correcting the alterations in diabetic rabbits caused by alloxan by increasing body weight, HDL levels and ascorbic acid (vitamin C) and decreasing LDL, VLDL, triglyceride, total cholesterol, Catalase and bilirubin levels. The effect of the oil is more expressive. [24] [25].

According to Jin and *al*, 2020, administration of *Ophiopogon* polysaccharide, *Notoginseng* total saponins and *Rhizoma Coptidis* alkaloids to rabbits with arteriosclerotic diabetes reduced blood glucose, glycosylated hemoglobin, glycosylated serum protein and fructosamine levels, and inhibited the enzyme aldose reductase and the AGE/RAGE pathway in the myocardium. In addition, these compounds reduced the expression of the pro-apoptotic: proteins p-Junk and Caspase-3 and increased the expression of the anti-apoptotic: protein Bcl-2. This demonstrates the ability of *Ophiopogon* polysaccharide, *Notoginseng* total saponins and *Rhizoma Coptidis* alkaloids to inhibit cardiac myocyte apoptosis [26].

A study of the effect of ethanolic extract of *Centratherum anthelminticum* seed showed that it had a hypoglycemic effect and reduced body weight in rabbits made diabetic by a fructose solution. In addition, the plant had a protective effect on the liver by normalizing biochemical parameters, in particular bilirubin and alanine aminotransferase. A reduction in glycated hemoglobin (HbA1c), uric acid and creatine kinase has also been observed. It also has a positive effect on oxidative stress by increasing levels of antioxidant enzymes and inhibiting lipid peroxidation [27].

Human model

In contrast to the high number of animal studies as a model, clinical trials in humans are still less than in animals.

In 2018, Panahi and *al* conducted a randomized, double-blind, placebo-controlled trial in 100 patients with type 2 diabetes for a period of 3 months to assess the effect of curcumin 500 mg/day in combination with piperine 5 mg/day, They found a positive effect on glycaemic and hepatic parameters, mainly a significant reduction in glucose, C-peptide, HbA1c, alanine aminotransferase and aspartate aminotransferase, while there was no significant difference in levels of C-reactive protein, a marker of inflammation, between the two groups [28]. In another randomized, double-blind, placebo-controlled study focused on the effects of curcuminoids (1000 mg/day) in combination with piperine (10 mg/day) on the lipid profile in 118 patients with type 2 diabetes for 12 weeks, showed that the curcuminoid group showed an improvement in lipid parameters compared with the placebo group, with a significant reduction in cholesterol, non-HDL-C and lipoprotein (a) levels and an increase in HDL-C levels, while triglyceride and LDL-C levels did not differ significantly between the two groups [29].

A randomized, triple-blind, placebo-controlled clinical trial using a parallel design conducted on 140 diabetic subjects who received daily either *cinnamon* bark powder or a placebo in 500 mg capsules twice daily for a period of 3 months, the results showed a significant improvement in anthropometric indices mainly a reduction in body mass, body fat and visceral fat; in addition, fasting glucose, HbA1c and postprandial glucose levels, as well as insulin levels and insulin resistance, were all reduced in the *cinnamon* group compared with the placebo. A significant reduction was also observed in total, HDL and LDL cholesterol levels, with the exception of triglyceride levels. Most of these changes were significantly greater in patients with a higher baseline BMI (BMI $\geq$ 27) [30]. A randomized, double-blind, controlled clinical trial of 36 diabetic patients (type 2), divided into two groups, one underwent an oral glucose tolerance test (OGTT) and the other underwent an ingestion of aqueous *cinnamon* extract (6 g/ 100ml) preceded by an OGTT. After measuring glucose levels, the researchers found that the extract did not significantly influence postprandial glycaemia [31]. In subjects with T2DM, a randomized, double-blind, controlled trial showed that supplementation with 3g of *cinnamon* extract for eight weeks did not significantly reduce NF-KB, IL-6, IL-8 and TNF-alpha [32].

A randomized, double-blind, placebo-controlled clinical trial of 72 participants with fasting blood glucose levels between 100 and 140 mg/dL showed that *ginseng* berry extract significantly reduced fasting blood glucose levels and 60-minute postprandial blood glucose levels in an oral glucose tolerance test after 12 weeks of treatment, but these effects remained non-significant on glycemic parameters [33]. In a study involving thirty type 2 diabetic patients in a randomized, placebo-controlled crossover trial lasting 12 weeks, the use of 6 g of

konjac-glucomannan fiber mixed with 3 g of American *ginseng* per day significantly reduced hemoglobin A1c (HbA1c) to below 0.31% and plasma lipids [34]. Vuksan and *al* conduct in 2019 a randomized, double-blind, placebo-controlled, crossover clinical trial on participants with type 2 diabetes lasting 8 weeks, these patients received either placebo or 3g/d of American ginseng extract at the same time as their original treatment, the researchers show that American ginseng significantly reduced HbA1c (-0. 29%, p=0.041), fasting glycaemia (-0.71 mmol/L, p=0.008) and systolic blood pressure (-5.6 mmHg, p<0.001) and an increase in serum nitrites (Nox) was observed (+1.85 ± 2.13 µmol/L; p<0.03). In addition, the beneficial changes did not affect the safety profiles [35].

A randomized crossover design study of healthy subjects given 200 ml of warm water or 200 ml of aqueous *Moringa Oleifera* extracts showed an improvement in antioxidant capacity as well as a reduction in plasma malondialdehyde levels with no remarkable effect on glycaemic profile [36]. In another prospective randomized placebo-controlled study, capsules of *Moringa Oleifera* leaf powder were given to diabetic patients (type 2), showing that there was no significant change in glycaemia and hemoglobin A1c [37]. In 2021, Gómez-Martínez and *al* tested the effect of a dietary supplement made from the leaves of *Moringa Oleifera* on randomized, double-blind, placebo-controlled pre-diabetic patients. After 12 weeks of the trial, they found a significant effect on blood sugar parameters, with a reduction in fasting blood sugar and a 58% reduction in hemoglobin A1c [38].

Also in this context of human patients' relevance, it is also worth to be mentioned that since there is an increased interest lately in the understating of the correlations that might exist between the metabolic and the neuropsychiatric dysfunctions [39] and considering our previous expertise in the neurobehavioral studies [40] and plant extrcts relevance in this context [41], our collaborative groups are presently working on a original study focusing on the possible protective effects of Marrubium vulgare extract on some sucrose induced-diabetic models of zebrafish.

Conclusions

Animal models and clinical trials are used to study diabetes and the use of natural molecules in the treatment of the disease. A number of ethanolic, aqueous and methanolic extracts from different parts of plants (seeds, leaves, etc.) are characterized by their hypoglycemic effect. This represents a major challenge for the treatment of chronic diseases and their use as adjuvants to ordinary hypoglycemic medicines or even as replacements for hypoglycemic medicines but still requires in-depth research to fully understand their mechanisms and avoid long-term side-effects.

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