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Potencial antidiabético de extractos de Higo (Ficus Carica) para el tratamiento de la diabetes mellitus tipo II

Antidiabetic potential of fig (Ficus carica) extracts for the treatment of type II diabetes mellitus

Potencial antidiabético de extratos de figo (Ficus carica) para o tratamento da diabetes mellitus tipo II

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Resumen

La medicina tradicional ha sido el apoyo de la humanidad durante cientos de años, brindando un sinfín de soluciones para diversas enfermedades al igual que una gran cantidad de beneficios nutricionales para la salud. Esta se enfoca en el uso de plantas medicinales, donde se puede encontrar un sin número de componentes químicos con propiedades medicinales únicas. En ese contexto, el higo, cuyo nombre científico es Ficus Carica, es una planta perteneciente a la familia Moraceae que ha sido utilizada en la medicina tradicional debido a su potencial farmacéutico. Este árbol de sabia lechosa, ramas dispersas, frutos en forma de pera y hojas similares a las de la papaya posee diversos componentes como fitoesteroles, flavonoides, aminoácidos, antocianinas, ácidos orgánicos, entre otros. Además, posee efectos antioxidantes anticancerígenos, antiinflamatorios e hipolipidémicos. Estos componentes son usados para el tratamiento de diversas afecciones endócrinas, respiratorias, gastrointestinales y reproductivas. De igual manera, brinda un excelente potencial antidiabético para disminuir la cantidad de glucosa en la sangre. Por esta razón, el objetivo de esta revisión es el análisis del potencial antidiabético de Ficus Carica contra la diabetes tipo II , determinar cuáles componentes generan dicho efecto, y describir nuevos tratamientos antidiabéticos naturales con una mayor eficiencia y menos efectos adversos.

Palabras Clave: Higo (Ficus Carica); planta medicinal; actividad antidiabética; medicina tradicional; diabetes tipo II.

Abstract

Traditional medicine has supported humanity for hundreds of years, providing countless solutions for various diseases as well as a wealth of nutritional health benefits. It focuses on the use of medicinal plants, where a number of chemical components with unique medicinal properties can be found. In this context, the fig, whose scientific name is Ficus carica, is a plant belonging to the Moraceae family that has been used in traditional medicine due to its pharmaceutical potential. This tree with milky sap, scattered branches, pear-shaped fruits, and papaya-like leaves possesses diverse components such as phytosterols, flavonoids, amino acids, anthocyanins, and organic acids, among others. It also has antioxidant, anticancer, anti-inflammatory, and lipid-lowering effects. These components are used to treat various endocrine, respiratory, gastrointestinal, and reproductive conditions. It also offers excellent antidiabetic potential by lowering blood glucose. For this reason, the objective of this review is to analyze the antidiabetic potential of Ficus Carica

against type II diabetes, determine which components generate this effect, and describe new natural antidiabetic treatments with greater efficiency and fewer adverse effects.

Keywords: Fig (Ficus carica); medicinal plant; antidiabetic activity; traditional medicine; type II diabetes.

Resumo

A medicina tradicional apoia a humanidade há centenas de anos, fornecendo inúmeras soluções para várias doenças, bem como uma riqueza de benefícios nutricionais para a saúde. Foca-se na utilização de plantas medicinais, onde se podem encontrar uma série de componentes químicos com propriedades medicinais únicas. Neste contexto, o figo, cujo nome científico é Ficus carica, é uma planta pertencente à família Moraceae que tem sido utilizada na medicina tradicional devido ao seu potencial farmacêutico. Esta árvore com seiva leitosa, ramos dispersos, frutos em forma de pera e folhas semelhantes à papaia possui diversos componentes, como fitoesteróis, flavonoides, aminoácidos, antocianinas e ácidos orgânicos, entre outros. Tem ainda efeitos antioxidantes, anticancerígenos, anti-inflamatórios e hipolipemiantes. Estes componentes são utilizados para tratar diversas condições endócrinas, respiratórias, gastrointestinais e reprodutivas. Oferece ainda um excelente potencial antidiabético, reduzindo a glicemia. Por este motivo, o objetivo desta revisão é analisar o potencial antidiabético do Ficus Carica contra a diabetes tipo II, determinar quais os componentes que geram este efeito e descrever novos tratamentos antidiabéticos naturais com maior eficácia e menos efeitos adversos.

Palavras-chave: Figueira (Ficus carica); planta medicinal; atividade antidiabética; medicina tradicional; diabetes tipo II.

Introducción

The prevention and treatment of metabolic diseases which affect the cardiovascular system are fundamental to ensure community's life quality. Type II diabetes (T-IID) is a chronic disease with high level prevalence and mortality worldwide which is increasing in epidemiological scale nowadays (Cordero et al., 2017). According to the International Diabetes Federation (IDF), approximately 700 million adults will be diagnosed with this disease by 2040 (Parissis et al., 2023). This affection produces the degeneration of β-cells in pancreas, avoiding the enough insulin release to metabolize glucose in the body, producing metabolic problems (Franco Quinde et al., 2018)

(Leahy, 2005). As a result, type II diabetes is the main cause of cardiovascular, cerebrovascular, renal diseases and non-traumatic amputations (Cordero et al., 2017) (DeFronzo et al., 2015). To fight against this disease, several treatments are used, taking drugs like metformine and insulin injections (Patel et al., 2023) (Bitew et al., 2021). Metformine reduces the basal hyperinsulinemia by diminishing the hepatic glucose production. It is also employed by prediabetic patients to avoid the development of the disease (Patel et https://orcid.org/0009-0000-9785-6494al., 2023). However, the prolonged use of this drug can produce renal damage and failure (Yang et al., 2014). In the case of insulin, it is an antidiabetic molecule involved in glucose absorption by tissues. This administration of this treatment is only required when patients do not have the capacity to produce enough insulin by themselves (Rodríguez, 2022). In Ecuador, metformine is one of the most used treatments by diabetic population. However, usually, there is a shortage of it in public health institutions, and diabetic Ecuadorian patients do not have enough economic resources to acquire it (Zavala Calahorrano & Fernández, 2018). On the other hand, insulin cannot be used in all diabetic patients due to their pancreatic function is good enough. For these reasons, research into novel and more effective treatments for diabetes control is fundamental to maintain population health and disease control. Based on the previous background, fig *(Ficus Caroca)* can be used as phytotherapy against type II diabetes due to its antihyperglycemic activity (Reyes-Castro et al., 2021). Some fig compounds like quercetin and dichloromethane can help to balance glucose levels in blood, protect pancreatic β-cells and ensure cardiovascular system capacity (Lin & Zhang, 2023). Therefore, this bibliographic review aims to determine which are fig extract benefits for human health, focusing on type II diabetes treatment to improve drug availability against this disease.

1. Fig *(Ficus Carica)* features and medicinal properties.

Ficus Carica is one of the most recognized plants around the world. Commonly known as “fig”, it is one of the favorite delicacies for their sweet flavor and soft texture. It belongs to *Moraceae* family, *Ficus* genus and *Carica* specie, reason why it displays characteristic papaya-like leaves (Badgujar et al., 2014) (Hj. Idrus et al., 2018) (Jabeen et al., 2023). This plant is native to Sub-Himalayan, and it can be grown in temperate climates (Badgujar et al., 2014) (Arsyad et al., 2022). Structurally, fig tree can reach 15–20 ft (9-12 m) in height and 10m wide. Morphologically, fig roots are shallow and fibrous whereas the trunk is made of soft wood which divides into massive spreading branches. Fig leaves are green, and they have a particular finger-chape of 3 to 5 segments (Figure 1) (Faramayuda et al., 2022). Fig fruit exhibits a pear shape, and they are placed axillary

on leafy branchlets. They can present several colors based on their maturation time between green and purple (Mohamad Hesam Shahrajabian et al., 2021). Finally, fig latex is a sticky solution composed of single cells. This milky exudate produces skin irritation due to several proteolytic enzymes (Faramayuda et al., 2022).

Figure 1: Fig leaves and fruit

Other distinctive structure is fig tree latex which is a milky white solution that contains a protein hydrolytic enzyme called ficin, which has pharmacological properties (Badgujar et al., 2014) (Barolo et al., 2014). Usually, fig fruit is used in dessert preparations and pigment industry. However, this plant can be used in wide research and industrial fields, especially in the pharmaceutical one, where have been used by traditional medicine over the years thanks to its several medicinal benefits (Mohamad Hesam Shahrajabian et al., 2021) (Dogara et al., 2024). It has been used to treat endocrine, respiratory, gastrointestinal and reproductive affections (Nuri & Uddin, 2020) (Arsyad et al., 2022). Moreover, it contains several amounts of vitamins, chemical compounds and nutrients to keep body's health high quality (Hj. Idrus et al., 2018). As well, figs are excellent sources of minerals, carbohydrates, lipids, enzymes and phenolics (Hajam & H, 2022). These molecules can be used pharmaceutically as antioxidant, anticancer, cytotoxic, anti-inflammatory and hypolipidemic agents (Hj. Idrus et al., 2018) (Kucukerdonmez et al., 2021) (Abdel-Rahman et al., 2021) (Mennane et al., 2021). More examples of medical uses of fig extracts are described in Table 1. Therefore, these properties can be used to improve people's health in the treatment of type II diabetes.

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N°	*Medical use*	*Type of extraction*	*Result*	*Plant part used*	*Reference*
1	Antipyretic	Ethanol extract	Reducing body temperature	Non mentioned	(Badgujar et al., 2014) (Nuri & Uddin, 2020)
2	Anti-inflammatory	Petroleum ether (PEE), chloroform (CE), and ethanol (EE) extracts	The EE exhibits greater anti-inflammatory effect	Leaves	(Nuri & Uddin, 2020) (Kebal et al., 2022)
3	Antispasmodic	The aqueous Ethanol extract	It produced relaxation in a spontaneous way	Fruit	(Badgujar et al., 2014) (Nuri & Uddin, 2020)
		Aqueous Ethanolic extract	Produced relaxation of spontaneous and low K+ (25 mM)- induced contractions with negligible effect on high K+ (80 mM) like that caused by cromakalim	Dried ripe fruits	(Murthy & Bapat, 2020)
4	Antiplatelet	The aqueous Ethanol extract	Inhibits the adenosine 5 0 - diphosphate and adrenaline-induced human platelet aggregation	Fruit	(Badgujar et al., 2014) (Nuri & Uddin, 2020)
		Aqueous Ethanolic extract	inhibited the adenosine 50 - diphosphate and adrenaline-induced human platelet aggregation	Dried ripe fruits	(Murthy & Bapat, 2020)
5	Antihelmintic	Aqueous, petroleum ether, chloroform, and methanol extr	Studied against Pheritima posthuma in comparison with mebebdazole as a standard drug	Leaves	(Badgujar et al., 2014)
6	Hepatoprotective	Methanol extract	Protective effect reflected by lowering the serum levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), total serum bilirubin, and malondialdehyde	Leaves	(Badgujar et al., 2014) (Nuri & Uddin, 2020)
		Phenolic fractions	Anti-hepatotoxic activity against carbon tetrachloride (CCl4) toxicity.	Dried fruit	(Murthy & Bapat, 2020)
7	Anticonstipation effect	Fig paste	Reductions in body weight and increased intestinal transit length	Fruit	(Badgujar et al., 2014) (Nuri & Uddin, 2020)
8	Hypoglycemic	Aqueous extract	Weight loss was prevented and increased plasma insulin levels.	Leaves	(Badgujar et al., 2014) (Nuri & Uddin, 2020)
9	Hypocholesterolemic activity	Chloroform extract	Decline in the levels of total cholesterol and decrease in the total cholesterol/HDL cholesterol ratio	Leaves	(Badgujar et al., 2014)
		Aqueous Ethanolic extract	Antihyperlipidemic potentials	Non mentioned	(Murthy & Bapat, 2020)
10	Anticancer effect	Fig latex	Palmitoyl derivative of AGS acts as the most potent inhibitor for various cancer cell lines	Latex	(Badgujar et al., 2014) (Nuri & Uddin, 2020)
11	Antioxidant effect	Dried figs	In vitro antioxidants after human consumption	Dried fruits	(Nuri & Uddin, 2020) (Murthy & Bapat, 2020)
		Ethanolic, methanolic and aqueous fig extractions	All solutions have a strong antioxidant power	fruit	(Dogara et al., 2024)
12	Antihypertensive	Aqueous Methanol extract	A dose-dependent decrease in the blood pressure and heart rate	Fruit	(Murthy & Bapat, 2020)
13	Antimicrobial	Aqueous extract Ethanol extract	Ethanol fig extract was active against all bacteria tested: *P. aeruginosa, staphylococcus aureus, E. coli and Klebsiella pneumoniae*.	Leaves	(Mennane et al., 2021)
14	Pro-fertility	Aqueous extract	The histology of the testes in Ficus carica treated rats revealed an improved cell arrangement in the germinal cell layer. Also, serum testosterone level showed an increment in the Ficus carica treatment group.	Fruit	(Mahanem et al., 2024)

15	Antifungal	Aqueous extract Ethanol extract	Ethanol fig extract was active against *candida albicans*.	Leaves	(Mennane et al., 2021)
		Aqueous extract Ethanol extract Methanolic extract Chlorophorm extract	Methanol and water both have little action against *Candida albicans.* Methanolic leaf extract was extremely effective against *Aspergillus niger*. Chloroform extract only demonstrated suppression on *Penicillium cyclopium* growth.	Leaves	(Dogara et al., 2024)
16	Anti-hypothyroidism	Ether extract	Ficus carica pet. ether extract recorded amelioration in all parameters suggesting its significance against thyroid hypothyroidism induced in male rats as prophylaxis and treatment	Leaves	(eL Batanony et al., 2024)
17	Pancreatic protection	Dichloromethane extract	Fig extract creates regular islets with a higher number of cells and uniform distribution, Also, islets showed a regular oval shape, with clear boundaries and a slightly larger volume. The degree of islet cell degeneration and necrosis was lighter.	Leaves	(Lin & Zhang, 2023)

Phytochemically, Ficus Carica contains several molecules like phytosterols, flavonoids, triterpenoid, amino acids, anthocyanins, organic acid, fatty acids, carbohydrates, phenolic components, aliphatic alcohols and secondary metabolites that are placed principally in its latex, leaves, root and fruit (Figure 2) (Badgujar et al., 2014) (Murthy & Bapat, 2020) (Rasool et al., 2023) (Hajam & H, 2022) (Fazel et al., 2024). As well, fig possesses phenolic acids like quercetin-3-O glucoside, 3-O- and 5-O-caffeoylquinic acid, ferulic acid, bergapten, psoralen and other organic acids (Hajam & H, 2022). More examples of secondary metabolites found in fig leaves extracts are coumarin, triterpenoids like lupeol acetate, oleanolic acid, bauerenol; aldehydes such as 2-methylbutanal; ketones: 6 methyl-5-hepten-2-one, monoterpenes and esters: ethyl salicylate, methyl salicylate, and methyl hexanoate (Faramayuda et al., 2022).

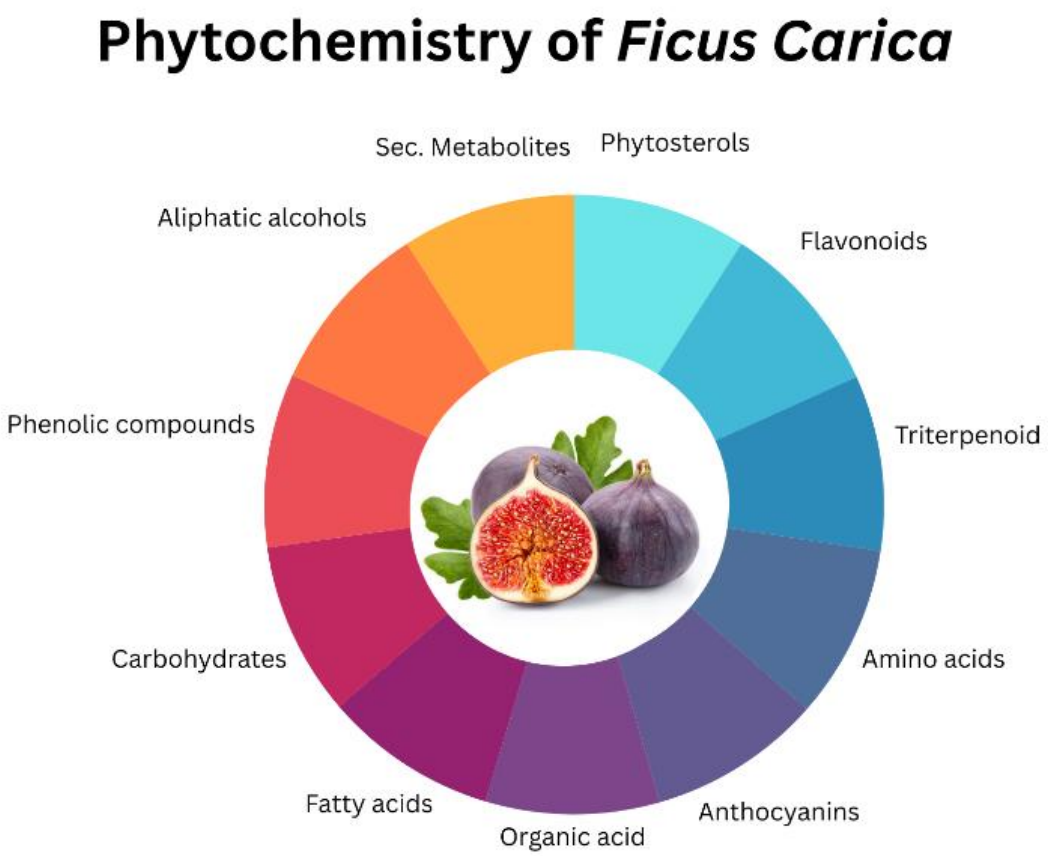

Figure 2: Phytochemistry of Ficus Carica-main compounds

2. Fig *(Ficus Carica)* application for diabetes type II treatment.

Traditional medicine has been a fundamental support to treat diseases in several cultures. For that reason, the use of plants as natural pharmacological agents is one of the most effective mechanisms to create new treatments without cytotoxicity and side effects (Priyoherianto & Saputra, 2018). One plant that has been used in traditional medicine over time is fig *(Ficus Carica)* thanks to its antioxidant, hepatoprotective, anti-inflammatory and hypoglycemic properties (Gupta et al., 2022). So, it can be considered as a candidate to be applied in phytotherapy to treat type II diabetic patients (Pérez et al., 2000). Nowadays, synthetic drugs used to treat this disease contain biguanides, sulfonylureas, thiazolidinediones, SGLT2 inhibitors and GLP-1 agonists (Gupta et al., 2022). These treatments can stabilize blood sugar levels, but unfortunately, they produce several side effects like insulin resistance, gastrointestinal adverse reactions, risk of edema, heart failure and weight gain when they are prolonged used (Gupta et al., 2022). For this reason, the creation of new

and novel natural drugs based on plant-derived substances with better pharmacological effects and less side effects is crucial.

3.1. Clinical trials features: population, goals and results.

Therefore, fig can be an excellent choice to create antidiabetic treatments (Pérez et al., 2000). To determine fig properties, the procurement of extracts from its leaves, fruit and seeds by decoction is required followed by clinical trials where these chemical solutions will be tested into diabetic rats. According to several researchers, aqueous fig leaves extracts (AFLE) have the capacity to decrease glucose levels. Also, they can contain active components that protect pancreatic cells (Gupta et al., 2022) (Stephen Irudayaraj et al., 2017). Other hypothesis supposes that these extracts have the capacity of minimizing insulin dosage. In the case of methanolic fig leaves extract (MeOH FL), they have the ability to attenuated pancreatic β-cell damage and inhibit α- glucosidase and α-amylase, which are enzymes responsible of blood sugar control and carbohydrate catabolism (Gupta et al., 2022). Other details related to clinical trials are shown in Table 2.

During experiments, several mice and rat models were employed to simulate the disease, expressing high glucose levels in blood, like a diabetic person. The induction of diabetes symptomatology was performed using drugs like alloxan monohydrate, Glibenclamide and streptozotocin (Aisyah et al., 2023; Gupta et al., 2022; Kurniawan & Yusuf, 2021; Lin & Zhang, 2023; Pérez et al., 2000; Priyoherianto & Saputra, 2018; Saleem et al., 2023). In terms of applied treatments, three main types of dilutants were employed: water for aqueous solutions, ethanol and methanol (Aisyah et al., 2023; Choi et al., 2024; Kurniawan & Yusuf, 2021; Mahanem et al., 2024; Pérez et al., 2000; Priyoherianto & Saputra, 2018; Saleem et al., 2023). Other studies employed Dichloromethane and Ethyl acetate (Gupta et al., 2022; Lin & Zhang, 2023; Stephen Irudayaraj et al., 2017). Doses applied during treatment vary in concentration, duration, number of doses and application mechanism. Finally, results described in all trials report the reduction of glucose levels in blood as well as protective effects in pancreas, cholesterol and triglycerides reduction, among others.

Table 2: Studies to determine antidiabetic properties of Fig extracts

N°	Fig extract	Population		Treatment		Effects searched	Results	citation
		Mice	Diabetic inductor	Concentration	Period			
1	Dichloromethane extract of Ficus carica leaves	SPF C57BL/6J male mice with high-fat diet	Streptozotocin (STZ,100 mg/kg)	500 and 1000 mg/kg	Daily per 6 weeks	Analyze anti-hyperglycemia potential in HepG2 cells	Lowers blood glucose and improves blood lipids and the pancreatic β-cell also tend to recover.	(Gupta et al., 2022)
2	Ethanol extract of fig leaves	Male rats strain Wistar	Alloxan 150 mg/kg intraperitoneally	40, 60 and 80 mg	14 days	A decrease in rat blood glucose levels	All doses reduce rats' blood glucose levels with statistically significant results	(Kurniawan & Yusuf, 2021)
3	70% ethanol maseration	Mice (Mus musculus)	Alloxan 180 mg / kg	100, 300 and 600 mg/kg	-----	Reduction effect of mice's blood sugar	Reduction effect of mice's blood sugar	(Priyoherianto & Saputra, 2018)
4	Aqueous extract	Adult female Wistar rats	Streptozotocin (65 mg/kg b.w.)	2.5 g/100 ml	Daily	Reduction of blood sugar.	Ficus carica extract showed a clear hypoglycaemic effect in diabetic rats	(Pérez et al., 2000)
5	Aqueous extract	Male Sprague-Dawley rats	streptozotocin (STZ) 50 mg/kg	400 mg/kg	Daily per 21 days	Study sperm quality, histology of the testes, serum testosterone and fasting blood glucose (FBG) level	The FBG level of the Ficus carica-treated rats exhibited a significant decrease compared to the negative control group	(Mahanem et al., 2024)
6	Dichloromethane extract	SPF C57BL/6J D mice with high-fat diet	Streptozotocin (STZ,100 mg/kg)	500 and 1000 mg/kg	6 weeks	Measurement of fasting blood glucose (FBG), blood lipids, oral glucose tolerance, glycated hemoglobin (HbA1c)	FCL extract lowers blood glucose and improves blood lipids and the pancreatic β-cell also tend to recover	(Lin & Zhang, 2023)
7	Ethanolic extract	Diabetic male mice (Mus musculus)	Alloxane 3.36 mg / 20 g / 0.5 ml / 20 g	5%, 10% and 15%	-----	Measurement of blood glucose levels	The most effective treatment to produce lower blood glucose was 15% concentration because it contains high content of flavonoids.	(Aisyah et al., 2023)
8	Ethanolic extract of fermented fig	Male ICR mice	-----	50, 125 and 250 mg/kg	8 weeks	The fasting blood glucose and intraperitoneal glucose tolerance test (IPGTT) was assessed.	FF is effective in reducing and inhibiting adipogenesis as well as lowering body weight, the blood glucose level, and lipid-related factors.	(Choi et al., 2024)

9	Ethanolic extract	Diabetic rat model	Alloxan monohydrate	400 mg/kg	6 weeks.	Analyze the therapeutic potential of dried fig and extract for their potential against hyperglycemia. Biochemical analysis such as fasting blood glucose (FBG), serum glucose, and insulin were performed.	The rat groups treated with dried fig fruit extract (G3) and 10 % dried fig fruit supplemented diet (G4) showed significant downregulation in FBG levels	(Saleem et al., 2023)
10	Ethyl acetate extract	Male albino Wistar rats with high-fat diet	Streptozotocin (STZ) (40mg/kg)	250 and 500 mg/kg	28 days	Blood glucose level, oral glucose tolerance (OGTT) and intraperitoneal insulin tolerance tests (ITT) were evaluated	The ethyl acetate extract (250 and 500mg/kg) of n F. carica leaves showed significant effect in the levels of blood glucose, total cholesterol (TC), triglycerides (TG), body weight and hep atic glycogen.	(Stephen Irudayaraj et al., 2017)

3.2. Clinical trials: experimental assay and statistic results

Results of some studies related to the antidiabetic effect of fig extracts are shown in Table 3. To analyze the hypoglycemic effects of fig extracts, several glucose parameters related to sugar levels were measured in blood samples using biochemical analysis. The tests include the analysis of fasting blood glucose (FBG) and serum glucose principally (Aisyah et al., 2023; Choi et al., 2024; Gupta et al., 2022; Kurniawan & Yusuf, 2021; Lin & Zhang, 2023; Pérez et al., 2000; Priyoherianto & Saputra, 2018; Saleem et al., 2023; Stephen Irudayaraj et al., 2017). Other studies complemented their analysis by studying other parameters like insulin measurements, glucose tolerance test, blood lipids, histological analysis, among others (Choi et al., 2024; Gupta et al., 2022; Lin & Zhang, 2023; Saleem et al., 2023).

During clinical trials, healthy rats were considered as a negative control group. By contrast, rats who were only exposed to drugs to induced diabetes were used as positive control to assess glucose values of diabetic patients. Kurniawan & Yusuf, 2021 describe glucose levels of 554 ± 47 mg/dl in their positive control. Other example was described by Saleen et al., 2023 where his positive group displayed 345.74±12.77 mg/dL glucose level. After the first glucose level evaluation, diabetic rats

were exposed to commercial drugs to determine chemical treatment effectiveness. Commercial drugs employed as antidiabetic treatments were Glibenclamide and Metformine. Some results of glucose levels reduction are described by Priyoherianto & Saputra, 2018 with a decrease of 44.3% using Glibenclamide; Mahanem et al., 2024 report a greatly reduction from 24.42±3.27 mmol/L to 13.22±0.81 mmol/L after 21 days of metformine treatment; Aisyah et al., 2023 indicate a decrease of 45.8% using Glibenclamide; Kurniawan & Yusuf, 2021 described a decrease of 30-40% of glucose levels approximately using metformine.

By contrast, fig extract used during trials were made of fig leaves and fruits. The doses applied during clinical assessments were different in each study and they depended on the authors. Also, all of fig treatments display similar antidiabetic effects compared to commercial diabetes treatments. So, they decreased glucose levels to normal or almost healthy rates. Evidence of the antidiabetic effect of fig extracts is described by Gupta et al., 2022 with a reduction of glucose in blood of 35.75% and 44.17% when he applied doses of 500 and 1000 mg/kg, respectively; Priyoherianto & Saputra, 2018 report blood reduction applying 100 mg/kg dose (17.3%), 300 mg/kg dose (29.3%), 600 mg/kg dose (35.2%); Aisyah et al., 2023 describe a reduction of 29.1%, 46.6% and 83.9% when rats are treated with 5%, 10% and 15% of fig extracts. Results of other clinical trials can be observed in Table 3. This comparison demonstrates that fig extracts have hypoglycemic potential, like chemical treatments. In addition, they present few or null side effects. The mechanism of action of fig-derived compounds is usually unknown, but researchers propose an undefined insulin-like peripheral effect (Pérez et al., 2000). Also, other beneficial features of fig extracts have been described during clinical trials are erythrocyte catalase level normalization and plasma vitamin E increase (Pérez et al., 2000). The statistical analysis employed ANOVA test due to the nature of the experiments with different p-values to express significant differences between positive control groups and those treated with fig extracts. Finally, all researches conclude that Ficus Carica extracts have a good antidiabetic potential with similar antidiabetic effects as commercial treatments. Also, they emphasize the importance of developing a mechanism to administrate correct dosages of fig leaves-derived compounds.

Table 3: Statistical results of clinical trials.

N°	Type of extraction	Plant part used	Controls		Statistical results				Side effects	Citation
			Negative	Positive	Glucose level before treatment	Glucose level after Treatment	P value	Significance		
1	Dichloromethane Extract	Dried leaves	Mice group fed with normal pellet diet	Diabetic mice with high fat diet treated with Pioglitazone	-----	500 mg/kg: 35.75%. 1000 mg/kg: 44.17%	P < 0.01	yes	None	(Gupta et al., 2022)
2	Ethanol extract of fig leaves	Leaves	Rats with alloxan without a cure	Rats with alloxan with metformin administration	20 g: 535 ± 20 mg/dl 40 g: 538 ± 15 mg/dl 60 g: 553 ± 24 mg/dl	20 g: 350 ± 20 mg/dl (32.3%) 40 g: 280 ± 15 mg/dl (47.9%) 60 g: 266 ± 24 mg/dl (51.8%)	p < 0.05	Yes	None	(Kurniawan & Yusuf, 2021)
3	70% ethanol maseration	Leaves	Healthy rats	Diabetic rats teated with Glibenclamide 0.65 mg/kg	100 mg/kg: 282.6±2.8 mg/dl 300 mg/kg: 281.0±1.0 mg/dl 600 mg/kg: 287.2±2.2 mg/dl	100 mg/kg: 233.6±5.4 mg/dl (17.3%) 300 mg/kg: 198.6± .0 mg/dl (29.3%) 600 mg/kg: 186.2± .8 mg/dl (35.2%)	p < 0.05	Yes	None	(Priyoherianto & Saputra, 2018)
4	Aqueous extract	Leaves	Healthy rats	Diabetic rats teated with Streptozotocin (65 mg/kg b.w.)	27.9 ± 4.5 mmol/l	19.6 ± 9.9 mmol/l	p<0.025	Yes	Plasma insulin levels were decreased in non-diabetic	(Pérez et al., 2000)
5	Aqueous extract	Fruit	Untreated diabetic rats	Diabetic rats treated with metformin (500 mg/kg)	16.78±3.44 mmol/l	10.08±1.67 mmol/l.	p < 0.05	Yes	None	(Mahanem et al., 2024)
6	Dichloromethane extract	Leaves	Normal healthy rats	Diabetic mice treated with Pioglitazone (20 mg/kg)	-----	500 mg/kg: 35.75%. 1000 mg/kg: 44.17%	P < 0.01	Yes	None	(Lin & Zhang, 2023)
7	Ethanolic extract	Leaves	Healthy rats	Diabetic rats teated with Glibenclamide and Na. CMC 1%	5% extract: 152 mg/dl 10% extract: 200 mg/dl 15% extract: 182 mg/dl	5% extract: 147 mg/dl (29.1%) 10% extract: 172 mg/dl (46.6%) 15% extract: 172 mg/dl (83.9%)	p < 0.05	Yes	Non specified	(Aisyah et al., 2023)
8	Ethanolic extract of fermented fig	Fruit	Rats with standard diet	Rats with high-fat diet	Control glucose: 124.4±3.4 mg/dl	50 mg/kg: 111.0±2.9 mg/dl 125 mg/kg: 114.2±3.9 mg/dl 250 mg/kg: 104.4±3.3 mg/dl	p<0.05	Yes	Non specified	(Choi et al., 2024)
9	Ethanolic extract	Fruit	Rats fed on the normal diet	Alloxanized diabetic rats fed on the normal diet	Positive control: 345.74±12.77 mg/dL Diabetic rats treated with	Diabetic rats treated with fig extract: 261.23±11.19 mg/dl	p<0.05	yes	Non specified	(Saleem et al., 2023)

					Glibenclamide: 284.42±10.41 mg/dL					
10	Ethyl acetate extract	Leaves	Rats treated with vehicle alone	Diabetic control rats treated with vehicle alone	Positive control: ~320 mg/dl	Rats treated with fig extract: ~250 mg/dl	p<0.005	yes	Non specified	(Stephen Irudayaraj et al., 2017)

1. Antidiabetic potential of flavonoids and additional fig benefits

Based on the previous sections, *Ficus Carica* has several substances with excellent medical properties, which can be employed as pharmaceutical treatments for diverse diseases, including type II diabetes. One of them are flavonoids, that are phenolic compounds synthesized by plants which usually give the orange-red colors to them (Dias et al., 2021). In *Ficus Carica*, the major flavonoids amount are in the fruit, and it is directly proportional to the maturation time (Rahmasita et al., 2021). Also, flavonoids can be found in other fig tree structures like leaves (Zhao et al., 2021). As therapeutic treatments, flavonoids have the capacity to modulate several enzymatic activities that can help human health. The most important medical potential of flavonoids is their excellent antioxidant activity (Jucá et al., 2020) (Ullah et al., 2020) (Pérez et al., 2003). Some other beneficial properties are their anti-inflammatory, antimicrobial, antiviral, antiparasitic and antifungal activities, and their cardioprotective efgfects (Jucá et al., 2020).

In the case of their antidiabetic effect, flavonoids present inhibitory effects of digestive enzymes, reduction of the glucose absorption and starch hydrolysis avoidance (Bitew et al., 2021). As a result, glucose levels decrease in blood. For this reason, flavonoids constitute one excellent candidate to be used as treatment against type II diabetes (Cahyana & Adiyanti, 2021) . In the case of the flavonoids inhibitory effect of digestive enzymes, they work on α-amylase and α-glucosidase, responsible of degrade carbohydrates in the mouth and intestine, respectively (Cahyana & Adiyanti, 2021). This inhibition happens by the bond between hydroxyl groups on flavonoids and enzyme catalytic residues (Hussain et al., 2020) (Shamsudin et al., 2022). Thus, the enzymatic activity decreases, reducing the amount of glucose metabolism, and hence, diminishing the amount of glucose that can be absorbed by the body. Consequently, the glucose level in blood will decrease. In the case of starch hydrolysis avoidance, flavonoids can form molecule complexes called “resistant starch” when they match natural starch (Cahyana & Adiyanti, 2021). As a result, this new starch complex is more resistant to degradation by digestive enzymes, reducing the amount of glucose available to be absorbed by the body. Finally, flavonoids can reduce glucose

absorption by the inhibition of glucose transporters SGLT and GLUT at the small intestine (Cahyana & Adiyanti, 2021) (Sok Yen et al., 2021). The reduction of channels opening decreases glucose entering, and consequently, the levels of blood glucose as well. The combination of these three effects gives an effective antidiabetic treatment. However, the main drawback is the multiple molecule interactions that flavonoids can have with other compounds due to their chemical structure, producing additional non desired effects (Cahyana & Adiyanti, 2021).

Based on previous information, several researches propose that fig extracts have hypoglycemic potential to create new antidiabetic treatments (Priyoherianto & Saputra, 2018). Clinical trials results evidence that fig-leaves/fruit-derived extracts reduce the amount of glucose levels in blood, which ensures health and homeostasis in diabetic patients (Gupta et al., 2022). Moreover, several studies propose flavonoids as the components responsible of the antidiabetic, anti-inflammatory and antioxidant activity (Cahyana & Adiyanti, 2021) (Jucá et al., 2020). Three antidiabetic mechanisms are mentioned as therapeutic effects of *Ficus Carica* being the inhibition of digestive enzymes (α-amylase and α-glucosidase), the reduction of starch hydrolysis by creating "starch resistant molecules" and blocking the use of glucose co-transporters (Cahyana & Adiyanti, 2021) (Sok Yen et al., 2021). All of them achieve the reduction of blood glucose levels in diabetic patients.

In the case of side effects, fig extracts are better than commercial antidiabetic drugs, showing few or null side effects. Hence, they are safety for patients' health. In the same way, other profitable pharmaceutical effects have appeared during trials like hepatoprotection and decrease of cholesterol in rats (Pérez et al., 2000). These properties can support diabetic patients, reducing risks of heart attacks and cerebrovascular diseases. Also, it can be used as supplementary treatment to support commercial ones. So, diabetic patients could decrease chemical antidiabetic drugs dosage uptake, and consequently, reduce side effects, and acquire additional cardiovascular benefits.

2. Conclusion.

Ficus Carica, commonly known as "fig", is a tree that belong to Moraceae family. It has several nutritive and pharmaceutical properties, becoming one of the most used medicinal plants worldwide. Structurally, it presents numerous spreading branches, pear-shaped fruit, milky latex and papaya-like leaves. All plant structures are used to obtain several molecules with potential pharmacological effects. Some examples are phytosterols, amino acids, anthocyanins, organic acid, among others. Usually, based on traditional medicine, fig is used to treat endocrine, respiratory,

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gastrointestinal and reproductive affections. Also, it can contribute with antioxidant, anticancer, cytotoxic, anti-inflammatory and hypolipidemic effects. In this review, the main pharmacologic effect studied was antidiabetic potential. When fig extract was used to treat type II diabetes, blood glucose levels decreased. Compared to chemical drugs like Metformin and Glibenclamide, fig extract shows similar antidiabetic effects. However, fig-derived treatment needs more concentration per dose to achieve similar effects as commercial treatments. By contrast, natural fig treatment presents less, or null side effects compared to chemical ones. Therefore, fig is an excellent source to obtain antidiabetic compounds to create new antidiabetic treatments because they can produce less side effects at high dose treatment concentration, having a similar effect like chemical therapies.

3. Future research and perspectives.

This review analyzes the antidiabetic potential of several compounds of fig extracts to be used as phytotherapy to treat type II diabetes. In future opportunities, the study of new applications of fig extracts can be performed, focused on diabetes during pregnancy or diabetes in animals because this natural treatment could be well tolerated by pregnant women and pets compared to commercial drugs.

Author contributions

All the authors contributed to the development of this project.

Conflict of interest

None

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