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High-sucrose diet induces diabetic-like phenotypes in *Drosophila melanogaster*: Protective effects of *Ficus carica* leaves.

Presented by:

- **Melle Boughagha Randa**
- **Melle Bouria Fairouz**
- **Melle Bousseliou Naama**
- **Melle Dridah Rimah**

Jury Members:

Ms. Labid A (MCA)	President	University of 20 August 1955 – Skikda
Mrs. Bezzar-Bendjazia R (MCA)	Promoter	University of 20 August 1955 – Skikda
Ms. Bouabdallah N (MCB)	Examiner	University of 20 August 1955 – Skikda

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Dedication

To the one whose prayers were the secret behind my success.

To my beloved mother, the source of endless love and care.

To my dear father, a symbol of strength, patience and unwavering support.

To my siblings, who stood by me through every step of this journey.

To all the members of my family, each and every one of you, for your constant love, encouragement and presence.

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I dedicate this work to you all, with deep gratitude and heartfelt appreciation.

Fairouz

Dedication

In the name of Allah, I am grateful to him …

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I deeply thankful to my parents, Dad Mourad and Mom Hafida for every sacrifice; every lesson; every moment of unconditional love, I am eternally grateful.

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To my little hero Açil, who brings joy to our home.

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Randa

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With all my heart, Rimah

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°C :	Degree Celsius
ADA:	American Diabetes Association
AKH :	Adipokinetic hormone
ACT:	Applied Knowledge Test
MRNA:	Messenger ribonucleic acid
ATP:	Adenosine Trisphosphate
CAT:	Catalase
CC:	Heart body
CHU:	University Hospital Center
***D*:**	*Drosophila*
DID :	Insulin-dependent diabetes
DILPs :	Drosophila Insulin-like Peptides
DM :	Diabetes mellitus
DNID :	Non-insulin-dependent diabetes
DT1 :	Type 1 diabetes
DT2 :	Type 2 diabetes
E20 :	20-hydroxyecdysone
EcR :	Nuclear receptors for ecdysteroids

***F. Charge* :**	*Ficus carica*
FID:	International Diabetes Federation
G:	Gram
GIP:	Glucose-dependentinsulinotropic polypeptide
GLP-1:	Glucagon-like peptide-1
GP :	Plasma Blood Glucose
GPJ :	Fasting plasma glucose
GPx :	Glutathione peroxidase
GS:	Glycogen synthase
GSK 3:	Glycogen synthase kinase-3
GST:	Glutathion S-Transferase
H :	Hour
HbA1c:	Glycated hemoglobin
OPTT:	Oral hyperglycemia
HIV:	*Human immunodeficiency virus*
HJ:	Juvenile hormone
HSD:	Honest Significant Difference
Hypertension:	The disease of high blood pressure
IL- 6R:	Interleukin-6 receptor
IL-6:	Interleukin-6
Impl2:	Late Imaginal Morphogenesis Protein 2

InR:	Insulin receptor
InRS1:	Insulin Receptor 1 Substrates
InRS2:	Insulin Receptor 2 Substrates
INSP:	National Institute of Public Health
CPI:	Insulin-producing cells
IR:	Insulin resistance
Keap1:	Kelch-like protein ECH 1
L:	Litre
L1:	First larval stage
L2:	Second instar larvae
L3:	Third instar larvae
MENA:	Middle East and North Africa
Mg:	Milligram
Mm:	Millimetre
FASHION:	Maturity-Onset Diabetes of the Young
Nrf2 :	Factor 2 Erythroid 2 Nuclear Factor
WHO:	World Health Organization
P85 :	Phosphotyrosine kinase regulatory subunit
PDK1 :	Phosphoinositide-dependent kinase 1
PIP :	Phosphatidylinositol phosphate
PPTH :	Phosphoponteteinyl hydrolase

PTEN : Phosphatase and TENsin homologue

SGLT2 : Sodium-glucose type 2

SOCS36E : Cytokine signaling suppressor 36E

SOD : Superoxide dismutase

TBC1D4: TBC1 domain family member 4

Upd2 : PTENLeptid-like to leptin

Upd3 : Unpaired 3 de type cytokine

Upds : Cytokine family unpaireds

Abstract

This study aims to investigate the antidiabetic effects of *Ficus carica* leaf extracts and metformin on *Drosophila melanogaster*, a widely used biological model for studying metabolic disturbances induced by a high-sucrose diet. The primary objective is to assess the impact of these treatments on food consumption and resistance to starvation in flies subjected to a hyperglycemic diet (30% sucrose), simulating metabolic disorders characteristic of diabetes.

The results indicate that prolonged exposure to this diet leads to a significant increase in food intake, coupled with a marked decrease in resistance to starvation, reflecting metabolic imbalance and impaired adaptive mechanisms to food deprivation.

Treatment with *Ficus carica* extracts, alone or combined with metformin, significantly reduced excessive food consumption while enhancing resistance to starvation. These interventions suggest a protective effect on energy regulation and metabolism in individuals experiencing metabolic stress due to excessive sucrose intake.

These findings highlight the potential of *Ficus carica* as a promising natural agent in managing metabolic complications associated with diabetes, providing a therapeutic alternative or complement to metformin.

Keywords: *Ficus carica*, *D. melanogaster*, diets high in sucrose 30%, antidiabetic effects.

Résumé

Cette étude vise à examiner les effets antidiabétiques des extraits de feuilles de *Ficus carica* et de la metformine sur *Drosophila melanogaster*, un modèle biologique largement utilisé pour étudier les perturbations métaboliques induites par un régime riche en sucrose. L'objectif principal est d'évaluer l'impact de ces traitements sur la consommation alimentaire et la résistance à la privation de nourriture chez des drosophiles soumises à un régime hyperglycémiant (30 % de sucrose), simulant les désordres métaboliques caractéristiques du diabète.

Les résultats montrent qu'une exposition prolongée à ce régime provoque une augmentation significative de la consommation alimentaire, accompagnée d'une diminution marquée de la résistance à la privation de nourriture, traduisant un déséquilibre métabolique et une altération des mécanismes d'adaptation à la faim.

Le traitement par les extraits de *Ficus carica*, seul ou en association avec la metformine, a significativement réduit la consommation excessive de nourriture tout en améliorant la résistance à la privation alimentaire. Ces interventions suggèrent un effet protecteur sur la régulation énergétique et le métabolisme chez les individus soumis à un stress métabolique lié à un apport excessif en sucrose.

Ces résultats mettent en évidence le potentiel de *Ficus carica* comme agent naturel prometteur dans la gestion des complications métaboliques associées au diabète, offrant une alternative ou un complément thérapeutique à la metformine.

Mots clés : *Ficus carica*, *D. melanogaster*, régime riche en sucrose 30%, effet antidiabétique.

ملخص

تهدف هذه الدراسة إلى دراسة التأثيرات المضادة لمرض السكر لمستخلصات أوراق اللبخ الكاريكا والميتفورمين على ذبابة الفاكهة السوداء، وهو نموذج بيولوجي يستخدم على نطاق واسع لدراسة الاضطرابات الأيضية الناجمة عن اتباع نظام غذائي غني بالسكروز .الهدف الرئيسي هو تقييم تأثير هذه العلاجات على استهلاك الغذاء ومقاومة الحرمان من الغذاء لدى محبي ذبابة الفاكهة الخاضعين لنظام غذائي عالي السكر (30% سكروز)، ومحاكاة الاضطرابات الأيضية المميزة لمرض السكري.

وأظهرت النتائج أن التعرض لفترات طويلة لهذا النظام الغذائي يؤدي إلى زيادة كبيرة في استهلاك الغذاء، مصحوبا بانخفاض ملحوظ في مقاومة الحرمان من الغذاء، وعدم التوازن الأيضي وتغير آليات التكيف مع الجوع.

أدى العلاج بمستخلصات شجرة التين الكاريكا، بمفردها أو بالاشتراك مع الميتفورمين، إلى تقليل الإفراط في تناول الطعام بشكل ملحوظ مع تحسين مقاومة الحرمان من الطعام .تشير هذه التدخلات إلى وجود تأثير وقائي على تنظيم الطاقة والتمثيل الغذائي لدى الأفراد المعرضين للإجهاد الأيضي المرتبط بالإفراط في تناول السكروز.

تسلط هذه النتائج الضوء على إمكانات شجرة التين الكاريكا كعامل طبيعي واعد في إدارة المضاعفات الأيضية المرتبطة بمرض السكري، حيث تقدم بديلاً علاجيًا أو مكملًا للميتفورمين.

الكلمات الرئيسية: *Ficus carica* ، *D. melanogaster*، نظام غذائي غني بالسكروز 30٪، تأثير مضاد للسكري

Introduction

Diabetes mellitus (DM) is a lifelong metabolic disease caused by multiple reasons, including genetics, environment, age, and lifestyle (Lancet, 1998; Luca and Ole F Sky, 2008). Patients with type 2 diabetes mellitus (T2D) account for 90% of all diabetics and this disease is characterized by insulin resistance (Chatterjee *et al*., 2017), which can lead to an increased risk of serious complications, including heart disease, diabetic nephropathy, retinopathy, diabetic arterial disease of the lower extremities, etc. (Forbes and Cooper, 2013). Existing oral hypoglycemic agents have drawbacks such as digestive discomfort, increased cardiovascular morbidity, and potential toxicities (Inzucchi *et al*., 2012). There is therefore a need for new, less toxic and highly effective anti-diabetic agents.

Natural products have been considered valuable sources for thousands of years. Traditional herbal medicines for the treatment of T2D and associated complications are particularly valuable due to their efficacy and minimal side effects (Chen and Wang, 2021; Unuofin and Lebelo, 2020). The concept of "medicine and food homology" suggests that certain foods may also have medicinal properties (Gong *et al.,* 2020).

Among the medicinal plants, the *Ficus carica* has been widely used since ancient times and has many health-promoting activities, such as antidiabetic, antioxidant, anti-obesity, anti-inflammatory, etc. These beneficial traits are due to various secondary metabolites, including phenolic acids, amino acids, hydrocarbons, fatty acids, volatile components, and other bioactive compounds. Latex contains a significant amount of these compounds, with some presence in leaves, fruits, and roots.

Many species of Ficus have been used for a variety of medicinal purposes in Siddha, Ayurvedic and Traditional Chinese medicine (Lansky *et al*., 2008). In addition, various pharmacological studies (e.g., anti-cancer, anti-inflammatory, and antidiabetic activities) have been supported by the ethnomedical uses of *Ficus* species (Lansky *et al*., 2008). Different organs of various species of *Ficus* have long been used by indigenous peoples around the world to effectively treat diseases, including diabetes. Over the past few decades, a number of studies have shown that crude extracts and compounds isolated from various species of *Ficus* (especially *F. benghalensis*, *F. religiosa*, *F. glumosa*, *F. deltoidea*, *F. racemosa,* and *F. carica*) exhibited potent antidiabetic properties in both in vitro and in vivo models. These Ficus species showed a

protective effect against streptozotocin- and alloxan-induced diabetic animals, which also attenuated all diabetes-related complications by inducing insulin secretion, inhibiting glucose absorption, increasing glucose uptake, and improving pancreatic β cell levels (Farsi *et al*., 2014, Irudayaraj *et al*., 2016, Ravichandra and Paarakh, 2014).

In recent years, the fly *Drosophila melanogaster* (*D. melanogaster*) has emerged as an advantageous alternative organism to mammalian models to explore different human pathologies, including metabolism-related disorders such as obesity and diabetes (Bharucha, 2009; Morris *et al*., 2012). Many biochemical mechanisms involved in the control of growth and metabolic processes in humans are present in the fly (Scott *et al*., 2004).

Of particular importance, the architecture and neuroendocrine mechanisms of *D. melanogaster* resemble those found in mammals (Rulifson *et al*. 2002). For example, *D. melanogaster* possesses insulin-producing cells (IPCs), insulin-like peptides (DILPs), and a receptor (InR); conserve molecular insulin/insulin-like growth factor signaling pathways (Musselman *et al*., 2011).

In this sense, data from the literature have shown that a diet rich in sucrose causes insulin resistance phenotypes in *D. melanogaster* that represent the pathophysiology of type 2 diabetes in humans (Morris *et al*., 2012; Pasco and Leopold, 2012). These phenotypes are normally characterized by elevated fat deposition and circulating glucose, systemic insulin resistance, shortened fecundity and lifespan in adult flies (Morris *et al*., 2012; Musselman *et al*., 2011; Pasco and Leopold, 2012; Pendse *et al*, 2013). In larvae, the insulin signaling cascade is involved in metabolic homeostasis and growth. Based on the fly system as an important genetic tool, studies have been conducted to investigate the possible interaction between caloric diets and gene expression on type 2 diabetes (Morris *et al*., 2012; Pendse *et al.,* 2013). Therefore, *D. melanogaster* represents an interesting organism model for studying diet-induced metabolic disorders and potential therapeutic strategies to address them.

Drosophila insulin-like peptides (DILPs) were first discovered in fruit flies in the 1970s (Duve *et al*., 1979). A fruit fly model of T2D was established using a high-sucrose diet, resulting in clinical manifestations similar to those of human patients with T2D, including slow growth and development, elevated blood glucose, obesity, and insulin resistance (Musselman *et al*.,

2011). These achievements provide a theoretical basis for the use of *Drosophila* as a model organism to study the pathogenesis of diabetes (Bai *et al*., 2018; Pereira *et al*., 2020).

The JAK/STAT cell signaling pathway mediates insulin resistance in mammals and in *D. melanogaster* (Jiang *et al*., 2009). In *Drosophila*, the Unpaireds (Upds) family of cytokines can activate the JAK/STAT signaling pathway. Upd2 (leptin-like peptide) and Upd3 (IL-6 analogue) (Oldefest *et al*., 2013) bind to the Dome receptor (IL-6R homologue), leading to the activation of the JAK/STAT pathway, which upregulates the expression of impl2 and socs36E. Impl2 prevents the insulin receptor (InR) from binding to Dilps, leading to insulin resistance (Ding *et al*., 2021). Socs36E disrupts insulin-induced phosphorylation of insulin receptor substrates 1 and 2 (InRS1 and InRS2) and promotes their degradation by ubiquitination, also leading to systemic insulin resistance (Galic *et al*., 2014; Ueki *et al*., 2004). In response to a high-calorie diet, the fat body secretes high levels of Upd2, Upd3, and Impl2, which can thus cause systematic resistance (Meng *et al*., 2022). Therefore, targeting the JAK/STAT pathway has therapeutic potential to treat T2D.

Objectives of the study

Due to the well-documented deleterious effects of a high-carbohydrate diet on metabolic homeostasis, we investigated the antidiabetic potential and underlying mechanisms of a medicinal plant known for its hypoglycemic properties, *Ficus carica*. To this end, we used *Drosophila melanogaster* as an experimental model to assess the impact of excessive sucrose intake on physiological responses analogous to those observed in type 2 diabetes, particularly in terms of food intake regulation and starvation resistance. Special attention was given to the analysis of feeding behavior using the MultiCAFE system, as well as to survival under fasting conditions—two parameters that are highly sensitive to metabolic disturbances associated with insulin resistance. The main objective of this study is therefore to determine whether administration of *Ficus carica* leaf extracts, alone or in combination with metformin, can correct the metabolic impairments induced by a high-sucrose diet by normalizing food intake and improving starvation tolerance. This work may contribute to a better understanding of the physiological effects of *Ficus carica* and support its potential use as a complementary therapeutic approach in the management of type 2 diabetes.

Bibliographic Research

I.1. General information on diabetes

I.1.1. Definition

The World Health Organization (WHO) defines diabetes as a serious chronic disease that occurs when the beta cells of the islets of Langerhans in the pancreas do not produce enough insulin or the body does not use that insulin properly (WHO, 2016).

Blood glucose levels must be kept tightly within a well-defined range to ensure the availability of this sugar as an energy source and to contextually prevent organ damage due to its excessive concentration. Glucose homeostasis is therefore based on the combined and opposite action of two hormones, insulin and glucagon, which, in mammals, are secreted by the beta and alpha pancreatic cells, respectively (Aronoff *et al.*, 2004).

I.1.2. History

The word "diabetes" is derived from the Greek word "dia-baino," which means "to go through." In the seventeenth century, the history of diabetes began, especially with Tomas Willis, who was one of the first to describe the presence of sugar in the urine of patients with diabetes. According to (Marcel, 1983), he makes a distinction between type 2 diabetic disease: diabetes mellitus is called "mellitus" and diabetes insipidus is called "insipidus". With the evolution of methods and techniques, the search for the mechanisms responsible for diabetes evolved from the eighteenth century onwards.

In 1775, the Englishmen Pool and Dobson revealed the presence of sugar in the urine of people with diabetes. However, it would take nearly 100 years, with the second half of the twentieth century, to have a precise understanding of the mechanisms that lead to the various forms of the disease (Guillausseau *et al*., 2003).

I.1.3. Epidemiology

I.1.3.a. Worldwide

It is a highly common disease with a high prevalence, mainly type 2 diabetes, which represents about 90% of all diabetics (Villar and Zaoui, 2010).

There are an estimated 537 million adults aged 20 to 79 worldwide (10.5% of all adults in this age group). It is projected that 643 million people and 783 million adults aged 20 to 79 will have diabetes by 2030 and 2045. So, while the world's population is projected to increase by 20% during this period, it is estimated that the number of people with diabetes will increase by 46% (IDF, 2021) (Figure 01).

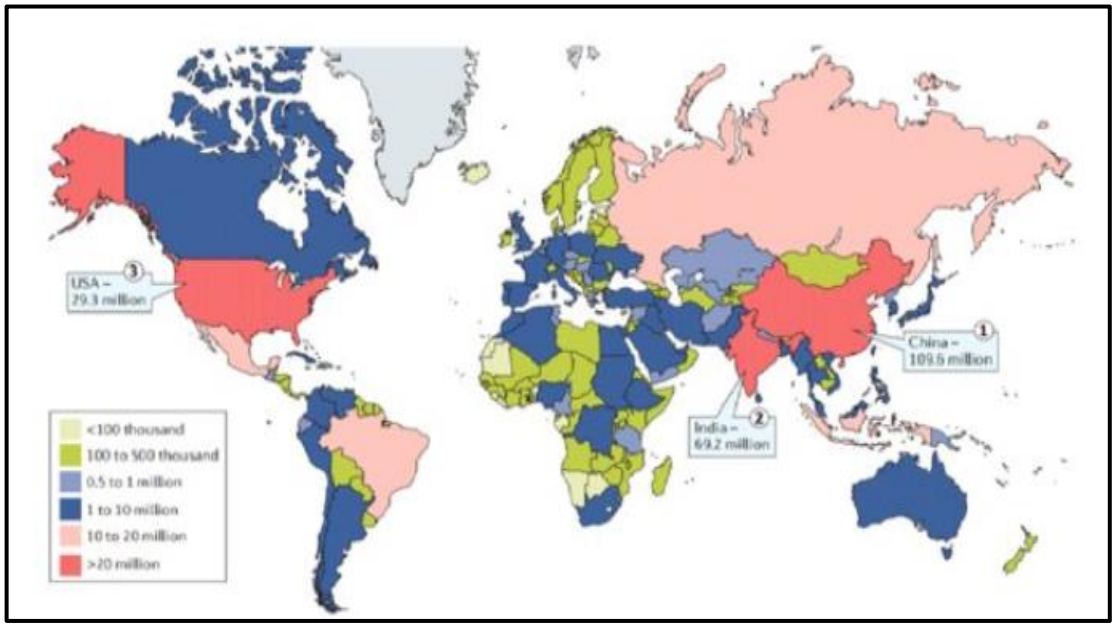

Figure 01: Estimated total number of adults (aged 20-79 years) with diabetes in 2021 (IDF, 2021).

Diabetes is estimated to be more common in women aged 20 to 79 than in men (10.2% vs. 10.8%). In 2021, more than 17.7 million men and women had diabetes (IDF, 2021) (Figure 02).

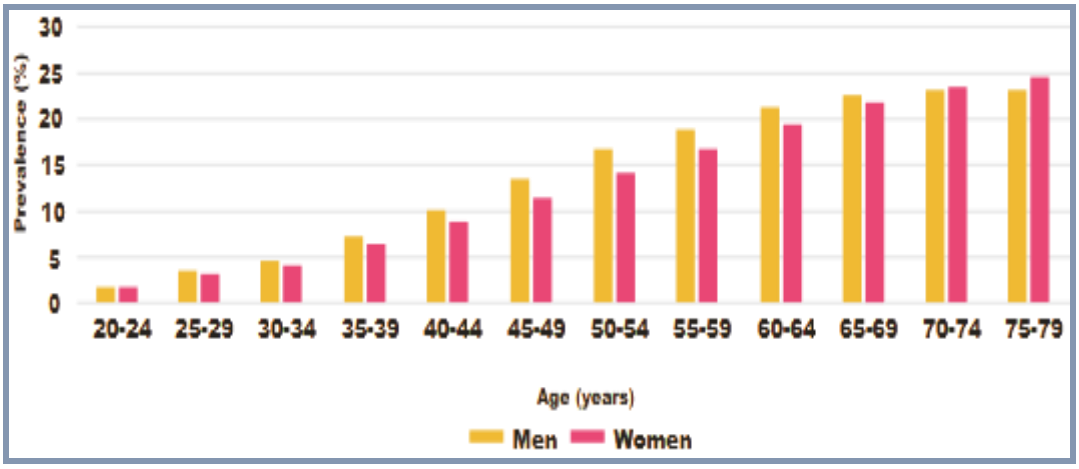

Figure 02: Analysis of the prevalence of diabetes among individuals aged 20 to 79 years in 2021.

I.1.3.b. In the Maghreb

The prevalence rate of prevalence studies conducted in the Maghreb, which is part of the MENA region, is respectively:

- ✓ In 2019, the prevalence of diabetes in Tunisia was 10.2% (55%), of which 75% were new cases of diabetes (Bouguerna *et al*., 2007). Another study in 2017 found a prevalence of 15.1% for diabetes and 5.9% for prediabetes (Ben Romdhane *et al*., 2014).
- ✓ 7.4% in Morocco, of which 42.8% were undiagnosed (FID, 2019). According to the report of the national survey *Stepswise (*2017-2018) on the prevalence of risk factors in Morocco, 10.6% of participants had diabetes and 10.4% had prediabetes.
- ✓ 9.7% in Libya, of which 42.8% have not been diagnosed, another study reveals a prevalence of 16.2%, 15.1% in women and 17.6% in men (FID, 2019).

I.1.3.c. In Algeria

- ✓ Type 2 ranks in Algeria among the non-communicable diseases in fourth place. (INSP, 2009).

✓ In 2016, the WHO published a report on diabetes and the risk elements related to it. In Algeria, the prevalence of males was 10.2 per cent and females was 10.7 per cent, for a total prevalence of 10.5 per cent. (WHO, 2016).

✓ According to the 2017 report of the International Diabetes Federation (IDF), the national prevalence of diabetes is 6.9% in Algeria. The margin of statistical uncertainty for individuals with diabetes in Algeria ranges from 1.25 to 2.45 million, corresponding to a national prevalence rate of 4.9 to 9.5 percent. (FID, 2017).

✓ From January 1, 1973 to December 31, 2017, there were 2358 new cases of T1D diagnosed in people under 15 years of age in the department of Oran (Touhami *et al*., 2019).

✓ From April 1 to October 31, 2020, 4537 patients were admitted to hospital for Covid-19 in the specialized structure of the Tlemcen University Hospital. 390 diabetics have been identified. (Lounici *et al*., 2021).

I.1.4. Classification

According to the etiology and pathophysiological mechanism, diabetes mellitus is classified into several entities. According to the ADA, WHO and the International Diabetes Federation (IDF), diabetes has been classified into:

I.1.4.a. Type 1 diabetes (juvenile diabetes)

It is known as insulin-dependent diabetes (IDD), an autoimmune disease. It manifests itself during childhood, adolescence or early adulthood before the age of 30, rarely in heavier people (Assal *et al*., 1994).

Hyperglycemia appears after the disappearance of more than 80% of β functional cells. The autoimmune process that causes pancreatic "insulitis" occurs on the pancreas. This autoimmune reaction occurs when there is genetic susceptibility, but can be caused by a variety of factors (Bluostone, 2010).

I.1.4.b. Type 2 diabetes

It is also known as non-insulin-dependent diabetes mellitus (N.I.D.) (WHO, 2016) or fatty diabetes because of its obesity. It usually occurs in people aged 40 and over, but it also occurs in young people due to obesity. Type 2 diabetes falls into two main categories:

- Insulin deficiency: When the cells of the pancreas do not produce enough insulin.
- Insulin resistance: occurs when the insulin produced does not work properly (Grimald, 2004).

Unlike type 1 diabetes, type 2 diabetes is most often asymptomatic, so a person with this type of diabetes can therefore live with the disease for several years without feeling it (WHO, 2016).

I.1.4.c. Gestational diabetes

It is a temporary condition that occurs during pregnancy and is linked to a long-term risk of type 2 diabetes (Bellamy *et al*., 2009). This occurs when blood sugar levels are higher than normal, but still below the threshold for diabetes. Women with diabetes during pregnancy and childbirth are at higher risk of complications, while their children are at higher risk of developing T2D in the later stages of their lives, which is usually diagnosed through prenatal screening and symptoms are not monitored (WHO, 2016).

I.1.4.d. Other specific types

- **Genetic defects in β cell function**

Maturity-Onset Diabetes of the Young (MODY) diabetes and neonatal diabetes are caused by monogenic mutations that affect the functioning of β cells. They account for less than 1 to 2% of all observed diabetes. (Johansson *et al*., 2017).

- **Genetic defect in insulin action**

Genetic alterations in insulin action can be caused either by a functional alteration of insulin receptors or by a decrease in the number of insulin receptors, mainly by mutations in the insulin receptor gene located on chromosome 19 (Banday *et al*., 2020).

- **Pancreatic diabetes (exocrine)**

All pathologies that affect the exocrine pancreas in general can lead to diabetes, but their impact on the overall incidence of diabetes is small, with less than 0.5% of all diabetes cases as (Banday *et al*., 2020; Ondy and Stolfi, 2016):

- Acute or chronic pancreatitis
- Cystic fibrosis.

- **Endocrinopathies**

Various endocrine disorders are characterized by an excessive secretion of hormones that partially or totally disrupt the action of insulin and can lead to diabetes, when secreted in excessive quantities such as:

- Growth hormone (hypersomatotropism).
- Cortisol (hypercorticism) (Banday *et al*., 2020).

- **Diabetes induced by drugs or toxins**

Several drugs have the ability to influence insulin production or secretion or tissue sensitivity to insulin. These drugs have the ability to induce diabetes or precipitate it in individuals who already have insulin resistance (Banday *et al*., 2020).

The most incriminated are:

- Corticosteroids (cortico-induced diabetes) (Petite, 2012).
- Anti-HIV treatments (Erickson *et al*., 2012).

- **Diabetes of infectious origin**

Covid 19 (Sultan and Halimi, 2021) and other viral causes such as: Hepatitis C

- **Other syndromes of genetic origin sometimes associated with diabetes**

- Klinefelter syndrome.
- Turner syndrome.
- Down syndrome..... (Feingold, 2019).

I.1.5. Pathophysiology of diabetes 2

The pathophysiology of type 2 diabetes involves many tissues and organs such as the pancreas, liver, skeletal muscle, adipose tissue, brain, gastrointestinal tract, and kidney (Figure 03). The decrease in insulin sensitivity (or insulin resistance) of liver, muscle, and adipose tissue cells combined with a long-term decrease in pancreatic cell function results in disrupted insulin production, resulting in hyperglycemia, which is characteristic of type 2 diabetes.

- **The pancreas**

Genetics is one of the mechanisms involved in reducing the functions of β-pancreatic cells. Several genes related to insulin and β cell degeneration have been identified in patients with type 2 diabetes (Grant *et al*., 2009).

Prolonged exposure of β cells to high glucose concentrations therefore affects their function and insulin production. The mechanisms of "glucotoxicity" are still unknown, but include definite impairment of insulin gene expression, oxidative stress, and catastrophic apoptosis of β cells (Poitout and Robertson, 2002).

- **The liver**

The liver plays a critical role in the synthesis of glucose in the body (Gerich *et al*., 2001), and type 2 diabetics experience an overproduction of glucose in the liver as it becomes resistant to insulin (Warram *et al*., 1990).

- **Muscle**

Patients with type 2 diabetes have resistance to insulin action due to defects in insulin signaling itself and low physical activity in general (Cusi *et al.,* 2000).

- **Adipose tissue**

Adipocytes are resistant to the antilipolytic effects of insulin in type 2 diabetics, resulting in an increase in free fatty acids. Gluconeogenesis increases, insulin resistance in the liver and muscles increases, and insulin secretion itself is impaired (Bays *et al*., 2004).

- **The brain**

The passage of insulin through the blood-brain barrier regulates the expression of various neuropeptides that play a role in food consumption and decreased appetite (Pagotto, 2009) and in type 2 diabetics, the brain can develop insulin resistance to the point that the appetite-suppressing effect of insulin is erased (Pagotto, 2009).

- **The gut**

The gut released from hormones called "glucagon-like peptide-1" (GLP-1) and glucose-dependent insulino tropic polypeptide (GIP) in response to nutrient ingestion (Freeman, 2009) and individuals with type 2 diabetes show a decrease in GLP-1 production and a reduced response to GIP.

- **The Nothing**

According to a recent study, it has been shown that the reabsorb ability of glucose by the kidney is increased in patients with type 2 diabetes compared to healthy people (DeFronzo *et al*., 2013), This leads to reabsorption of excess glucose and its return to the circulation in patients with type 2 diabetes, which can lead to an increase in hyperglycemia.

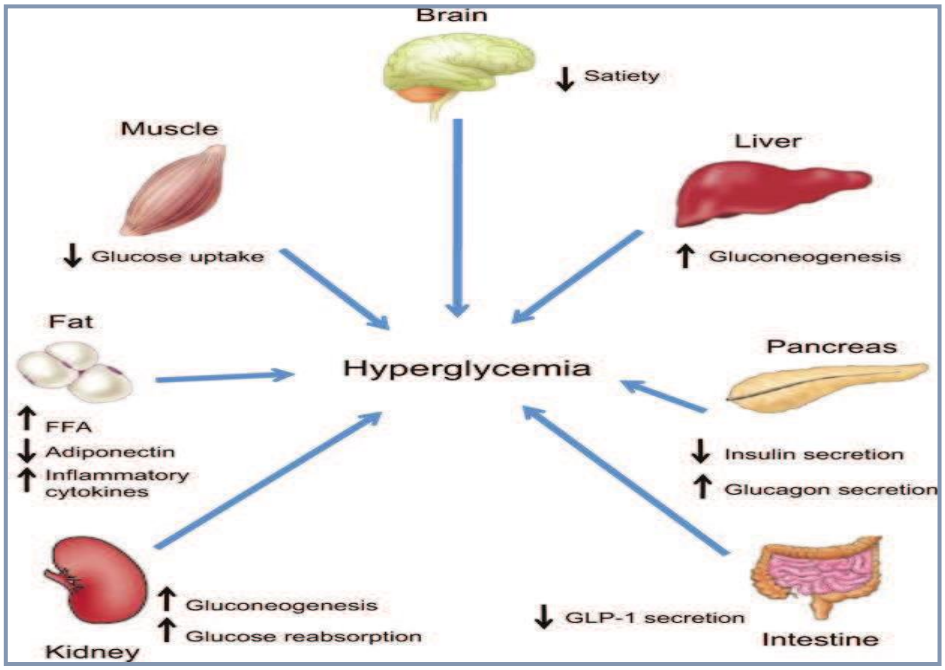

Figure 03: Pathophysiology of diabetes 2 (After Cornell S.).

I.1.6. Risk factors

Different factors, such as genetic and environmental factors, have an impact on the action of insulin.

I.1.6.a. Genetic factors

Most patients with type 2 diabetes have a disease that is genetically inherited polygenically and has no clear genetic cause. The insulin gene and the insulin receptor are the first to be mutated (Ostensonet, 2001).

I.1.6.b. Environmental Factors

Include various elements such as (Crabbé *et al*., 2010):

- Obesity.
- Age
- Stress
- Alcohol and tobacco consumption.
- High Blood Pressure (Hypertension)
- The distribution of fats in the abdomen, subcutaneous and visceral.

I.1.7. Insulin Resistance

Insulin is a 51-amino acid peptide hormone secreted by the β cells of the pancreas in response to high blood glucose levels. In 1921, Banting and Best discovered it in collaboration with their colleagues Collip and Macleod (Cohen, 2006).

Insulin resistance is an in vivo biological reaction that manifests itself as a decrease in insulin secretion or a defective action. Non-insulin-dependent diabetes has a feature that affects most of the target tissues, such as the liver which increases its glucose production, skeletal muscle, and adipose tissue. The mechanisms responsible may be found at various levels of insulin metabolism, including at the insulin receptor level of target cells (Buysschaert *et al.*, 1999; Raccah 2004) (Figure 04).

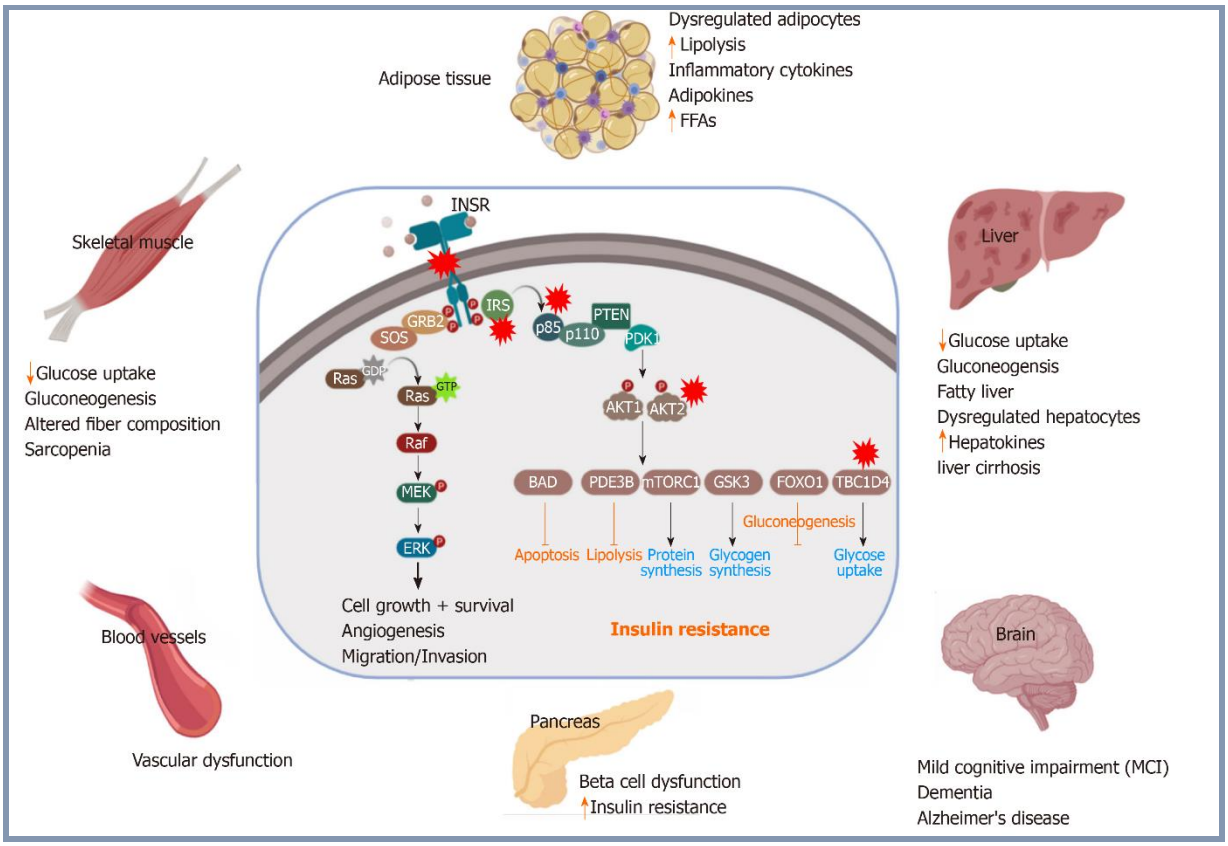

Figure 04: Consequences and pathological effect of insulin resistance (Elsayed *et al*., 2021). Insulin resistance (IR) in insulin target tissues can be caused by genetic alterations and mutations in the insulin signaling pathway. The red stars represent reported genetic abnormalities, such as insulin receptor, insulin receptor substrates, p85, AKT, and TBC1D4. In response to the insulin response, targeted insulin tissues (adipose tissue, skeletal muscle, liver, pancreas, brain, and blood vessels) manifest activation of catabolic processes and accumulation of toxic metabolic byproducts as well as inflammatory cytokines, leading to β-pancreatic cellular dysfunction and other metabolic disorders (Elsayed *et al*., 2021).

I.1.8. Dysfunction of β cells

Type 2 diabetes is not only manifested by an alteration in peripheral insulin sensitivity, but also and to the same extent by a dysfunction of functional β cells. Currently, it is recognized that in type 2 diabetes, there are intrinsic defects in insulin secretion and production at the level of the cells β themselves, which prevents sustained (additional) insulin secretion to overcome insulin

resistance (Palitzsch and Bellheimer, 2000; Kahn, 1998) and leads to progressive failure of β cell function. Damage to ß-pancreatic cells is primarily caused by glucotoxicity and lipotoxicity (Chang-Chen *et al.,* 2008).

"Glucotoxicity" is caused by mechanisms such as definite impairment of insulin gene expression, oxidative stress, and systemic apoptosis of β cells (Poitout and Robertson, 2002) (Figure 05).

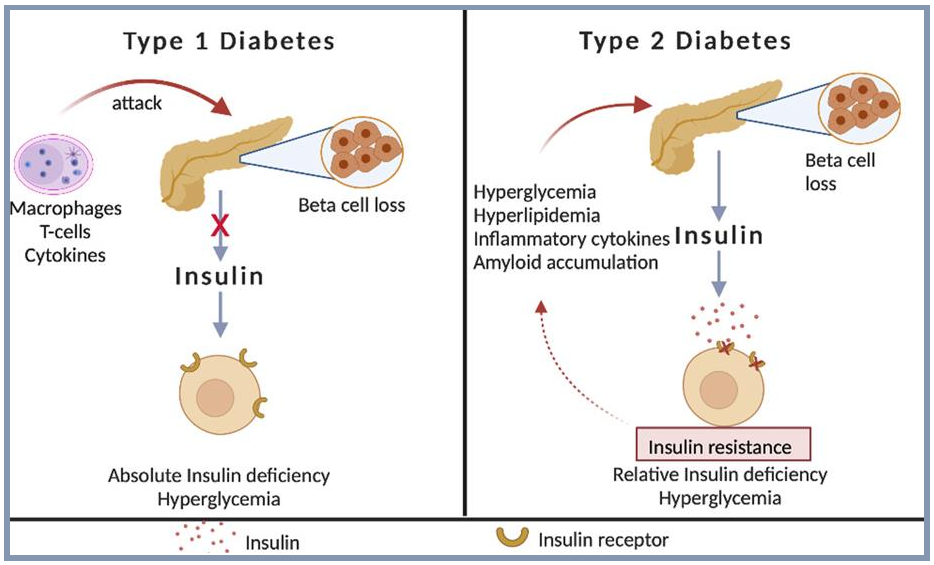

Figure 05: Consequences of type 1 and type 2 diabetes (Khin *et al*., 2023). In type 1 diabetes, the β cells of the pancreas are destroyed by immune cells, such as T lymphocytes, macrophages and cytokines produced by these immune cells, resulting in total insulin deficiency and therefore hyperglycemia. Hyperglycemia, hyperlipidemia, cytokines, and amyloids are factors that alter pancreatic β cells in type 2 diabetes. If insulin is produced by pancreatic cells β, insulin levels are insufficient to compensate for insulin resistance, resulting in relative insulin deficiency and hyperglycemia (Khin *et al*., 2023).

I.1.9. Complications

Complications caused by both types of diabetes can affect different parts of the body. Two main categories are identified: acute complications and chronic complications.

I.1.9.a. Acute complications

- **Diabetic ketoacidosis**

A complication commonly associated with type 1 diabetes, but sometimes seen in type 2 diabetes (Bougle, 2014), when there is a total or relative decrease in insulin production (Monnier *et al*., 2018), as insulin prevents the synthesis of ketone bodies and can lead to a serious clinical condition known as ketoacidosis (Fink and Mikesky, 2018).

- **Lactic acidosis**

It is due to an accumulation of lactic acid by increases in its production in decreasing its use (Monnier *et al*., 2018), Metformin treatment by preventing the entry of lactate (Belmin *et al*., 2016).

- **Hyperosmolar coma**

This complication occurs in people with type 2 diabetes (Landrieu *et al*., 2018). It is distinguished by an increase in blood sugar, often greater than 5 g/L, which leads to an increase in the concentration of glucose in the blood and dehydration (Monnier *et al*., 2018).

- **Hypoglycemic coma**

It is a complication present in patients with type 1 and type 2 diabetes (Landrieu *et al*., 2018). It is due to a relatively large glut of insulin in the blood, with exceptionally low blood sugar levels (Ectors, 2015). Venous blood glucose is defined as less than or equal to 0.70 g/L (3.9 mmol/L) (Monnier *et al*., 2018).

I.1.9.b. Chronic Complications

There are two types of chronic complications of diabetes, namely microvascular and macrovascular.

Microvascular complications

- Nephropathy (kidneys).
- Retinopathy (eyes).
- Neuropathy (nerves).

Macrovascular complications

- Heart disease.
- Cerebrovascular accident (brain).
- Peripheral arterial disease (feet and others) are the main macrovascular complications that are responsible for morbidity and mortality in diabetics (Monnier *et al*., 2018).

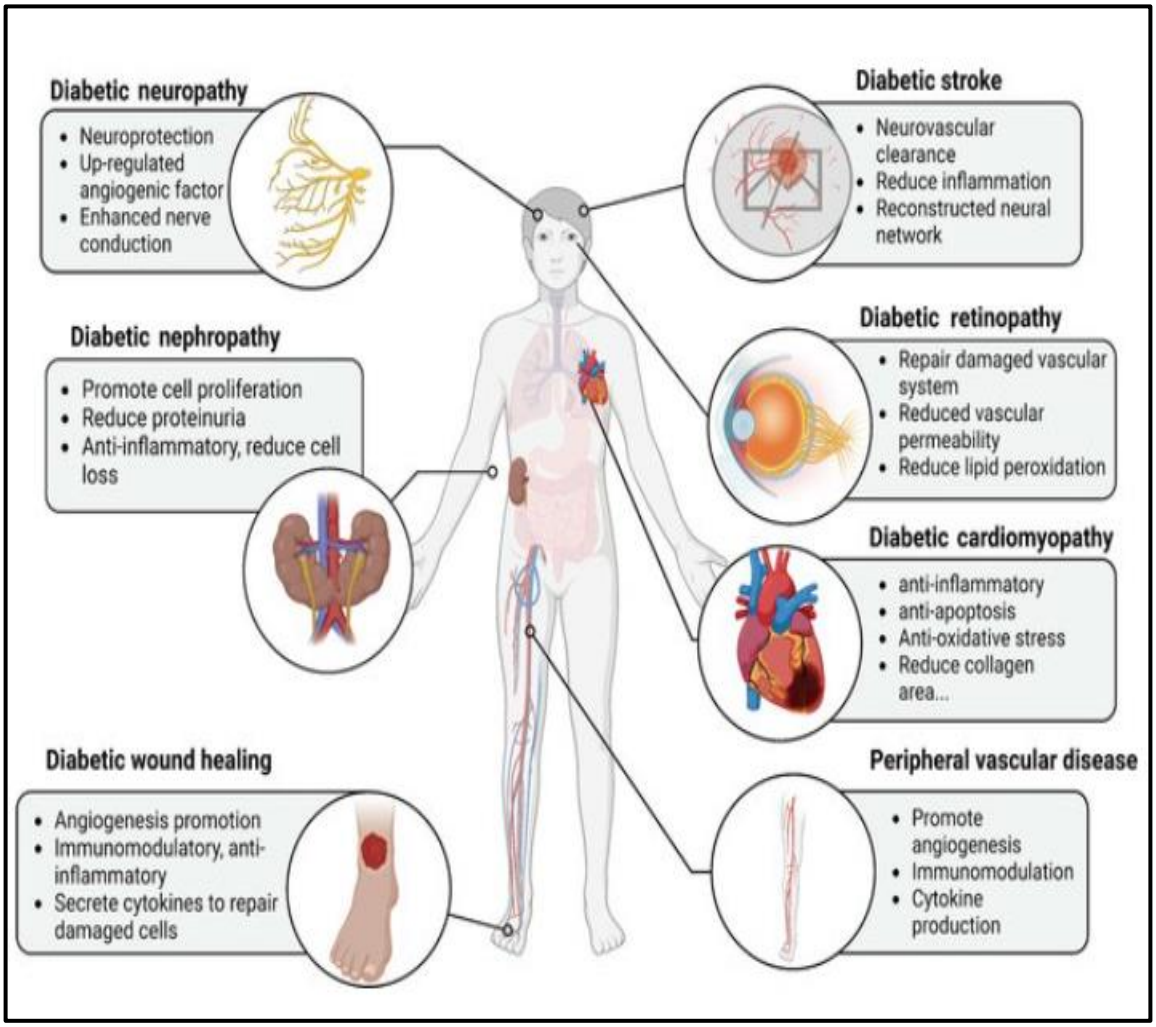

Figure 06: Major complications of diabetes (IDF, 2013).

I.1.10. Diagnosis

More than 100 years ago, methods for measuring blood glucose were developed. Today, the diagnosis of diabetes is based primarily on three distinct elements:

- ✓ Fasting plasma glucose (GPD).
- ✓ Plasma glucose 2 hours after an oral glucose load (OGTT).
- ✓ Glycated hemoglobin (Hba1c).

Each approach provides data on glucose physiology and metabolism:

- ✓ GPJ illustrates post-absorptive glucose homeostasis (Bergman *et al*., 2020).
- ✓ OGTT essentially illustrates the removal of an exogenous glucose load (Defronzo, 2009).
- ✓ HbA1c, on the other hand, corresponds to the overall average glycemic of the 2 to 3 months preceding the sampling.

Table 01: Criteria for diagnosing diabetes (ADA, 2021).

GPD≥ 1.26 g/l (After fasting for at least 8 hours) *
Or
GP≥ 2.0 g/L 2 hours after oral hyperglycemia (OGTT)*
Or
HbA1c≥ 6.5% test done by a certified and standardized method*
Or
GP≥ 2 g/l at any time of the day in a symptomatic patient

* In the absence of clear symptoms of hyperglycemia, the diagnosis requires two pathological assessments, either on the same sample or on two different samples.

I.1.11. Processing

The patient with diabetes requires an appropriate therapeutic approach. The goal of management is to suppress the clinical symptoms associated with hyperglycemia and to prevent

complications associated with diabetes mellitus, treatment, or the occurrence of multiple diseases (inflammatory, infectious, neoplastic, or hormonal in nature).

- **Hygienic and dietary treatments**

The implementation of these measures is essential to treat T2D. They have been clearly confirmed to prevent T2D in a good quality randomized study such as: diet and physical activity (Tuomilehto *et al*., 2001).

- **Insulin therapy**

The principle of insulin therapy is to replace the missing insulin with daily injections of exogenous insulin, the quantity of which is determined beforehand according to blood glucose levels (Feldman, 2003; Mohn *et al*., 2012).

- **Oral antidiabetic medications**

Current drug treatments target the various metabolic abnormalities seen in patients with type 2 diabetes. Oral antidiabetic drugs are classified into two broad categories: insulin sensitizers and insulin secretagogues (Tielmans *et al.,* 2007).

For decades, the solution was easy, as there were only sulfonylureas and insulin. This was followed by the appearance of interintestinal α-glucosidase inhibitors, glitazones, glinides, drugs with an incretin effect and, most recently, sodium-glucose cotransporter type 2 (SGLT2) inhibitors (Fery, 2014; Scheen, 2015)

Metformin is a biguanide that is currently the most common antidiabetic drug used to treat type 2 diabetes. This success is the result of several elements: its effectiveness, its occupational safety, its tolerance and its low manufacturing cost. Metformin acts primarily on the liver, where it moderates the inhibition of complex I of the mitochondrial respiratory chain. This leads to a decrease in the energy load of the liver, which leads to a decrease in glucose production by the liver (Marc *et al*., 2014; Scheen, 2015).

I.2. Presentation of the biological species

I.2.1. Drosophila: model organism

The fruit fly, better known as the "fruit fly", is a holometabole brachycerous dipteran insect. *Drosophila melanogaster* (Meigen, 1830) is the organism of choice for biological research, used as a model organism for more than a century. Originally, this organism was mainly studied in genetics to understand the rules of inheritance of traits. After Thomas Hunt Morgan in 1933 for his work on the role of chromosomes in heredity, three fruit drosophilists (E.B. Lewis, C. Nüsslein-Volhard and E. Wieschaus) were awarded the Nobel Prize in Medicine in 1995 for the genetic control of early embryonic development in *Drosophila*. Recently, another Nobel Prize was awarded to J.A. Hoffman for his research in immunology. Today, *Drosophila* is mainly used in developmental biology (Gilbert *et al*., 2013), to understand how a complex organism is formed from a fertilized egg, but also in the neurogenetics of learning (Dukas, 2008). In addition to the importance of Drosophila in the various fields of biology, this fly has many advantages, including a genome that has been fully sequenced since 2000 (Adams *et al.,* 2000) which allows the use of many molecular tools. In addition, the easy maintenance of farms in the laboratory, combined with a short life cycle (10 days at 25°C) and abundant offspring available in each generation, represents a significant advantage.

I.2.2. Taxonomy

Fruit flies are animals belonging to the phylum arthropods and more precisely to the class of insects. They belong to the order of Diptera (or true flies) characterized by the presence of dumbbells on the third thoracic segment, which are essential for the stabilization of flight. This order includes flies, midges and mosquitoes. The *Drosophilidae* family has nearly 3000 species (O'Grady and Markow, 2009) that have colonized all types of environments (Figure 07). The majority of its species belong to the two subgenera: *Drosophila* (1450 species) and *Sophophora* (450 species) (Figure 08). Following recent studies, it would seem that *D. melanogaster* is more phylogenetically related to the genus *Sophophora* than to the genus *Drosophila* (O'Grady and Markow, 2009). The inclusion of *melanogaster* in the genus *Sophophora* was proposed to the International Commission on Zoological Nomenclature, which sparked a long debate and

dissatisfaction among many fruit drosophilists who consider *D. melangaster* to be the most famous species after *Homo sapiens* (Dalton, 2010).

Règne	*Animalia*
Embranchement	*Arthropoda*
Sous- embranchement	*Hexapoda*
Classe	*Insecta*
Sous-classe	*Pterygota*
Infraclasse	*Neoptera*
Ordre	*Diptera*
Sous- ordre	*Brachycera*
Infra- ordre	*Muscomorpha*
Famille	*Drosophilidae*
Sous- famille	*Drosophilinae*
Genre	*Drosophila*
Espèce	*Drosophila melanogaster* **Meigen, 1830**

Figure 07: Taxonomy of *Drosophila melanogaster*.

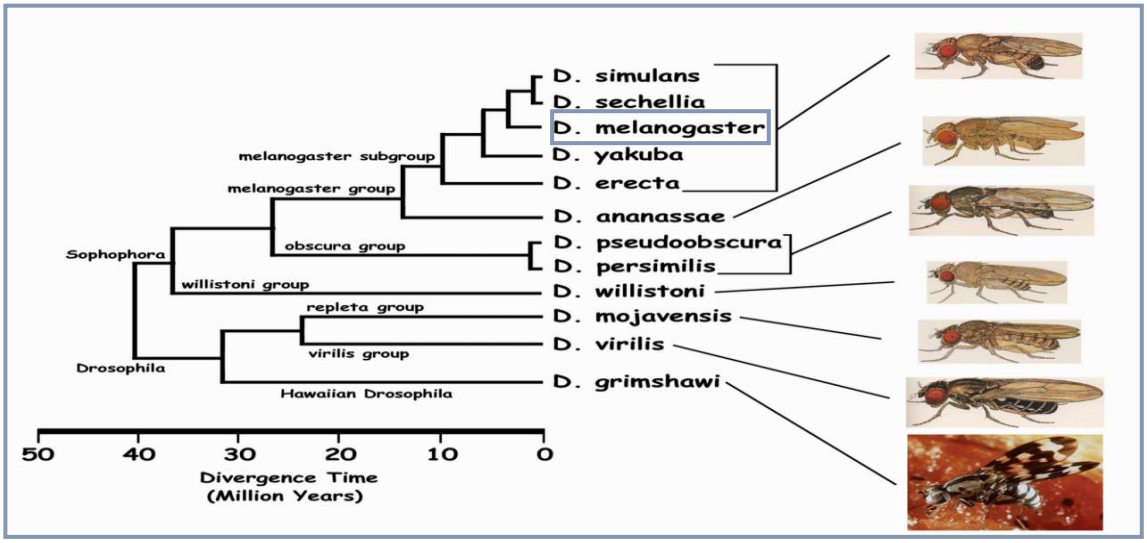

Figure 08: Phylogeny of Drosophila melanogaster (O'Grady and Markow, 2009).
Diagram: (http://hereditariedadgenetica.blogspot.com/2008/03/taxonomia.html).

I.2.3. Main characteristics of *Drosophila melanogaster*

Fruit flies exhibit sexual dimorphism (Parvathi *et al*., 2009) and to differentiate males and females, several traits can be considered:

Fly Size: This is the first and most basic step in distinguishing the sex of *Drosophila*. This is because female flies tend to be much larger than male flies (the female is about 25% larger than the male). (Fig. 09).

Shape and color of the abdomen: The tip of the abdomen is elongated in females and a little more rounded in males. The abdomen of a fly is made up of many different segments. On a male fly, the last two segments of the abdomen are much darker than the female. Males have thick black bands, while females tend to have a dark stripe on the bottom with a lighter stripe on top (Fig. 09).

Presence of sex combs: Males have what have been called sex combs, a fringe of about ten valiant black hairs on the distal side of the base of the front leg. These hairs are absent in females (Parvathi *et al*., 2009) (Fig. 09).

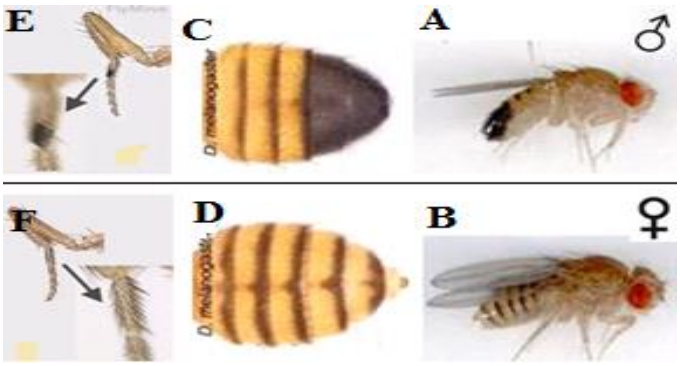

Figure 09. (A): *D. melanogaster* male: Gr: ×12.08. **(B):** *D. melanogaster* female: Gr: ×9,11. **(C):** Abdomen pointed and dark (male). **(D):** Rounded and pale abdomen (female). **(E):** Sex combs (male). **(F):** Absence of sex combs (female).

(https://planet-vie.ens.fr/article/1456/elevage-mouche-vinaigre-drosophila-melanogaster)

I.2.4. Life history

As a holometabolous insect, *Drosophila melanogaster* undergoes several drastic changes in the body plane throughout its life. After hatching, its larval development consists of three stages and is characterized by strong feeding activity. The last larval stage stops feeding, stops to form a pupa The insect then undergoes a metamorphosis (complete transformation) gradually transforming its larval organism into an adult organism. Upon emergence, the imago begins to feed again. He still goes through a phase of 8 to 12 hours of immaturity where his nervous system finishes developing, then the new adult becomes sexually mature and engages in reproduction (Dubrovsky, 2007) (Figure 10).

The life cycle of *D. melanogaster* includes an embryonic stage (eggs), three larval stages, a pupal or pupal stage, and an adult stage where the insect is able to fly and reproduce (Figure 10).

- **Embryonic stage**: The female lays hundreds of eggs on rotting fruit or other moist or fermenting matter (Tavernier and Lizeaux 2002). The eggs are shaped like a rugby ball and are whitish in colour and are about 0.5 mm long.
- **Larval stage**: About twenty-three hours after laying, the eggs will hatch to give birth to a whitish larva called a "maggot". The latter then feeds on the pulp of the fruit by digging galleries. The larval stage lasts 4 days and includes three stages: L1 (24 h), L2 (24 h) and L3 (48 h). At the end of this stage (110 h after laying), the 3rd instar larvae stop feeding, leave the nutrient environment and begin a wandering phase. At the end of the process, the larvae secrete a glue and attach themselves to a support (Dubrovsky, 2007).
- **Pupal stage**: The eversion of the anterior spiracles 120 h after laying defines the beginning of the prepupal stage, which will last 12 hours. The last larval cuticle quickly tans and becomes the puparium, in which the metamorphosis will take place. The latter continues during the 3 and a half days of the pupal period and at the end the larval tissues have been histolysed and the adult structures have formed from the imaginal discs (Compbel, 2006; Quinn *et al*., 2012) (Figure 09).
- **Adult stage**: At the end of the pupal stage, the young adult fruit fly not yet pigmented emerges from the pupa and after 8 hours the pigmentation is complete and the wings are

swollen. Adults feed on ripe or spoiled fruit. Females are sexually mature about 12 hours after emerging from their pupae. They store sperm from males to which they have mated for later use and begin laying eggs a day later (Tavernier and Lizeaux 2002).

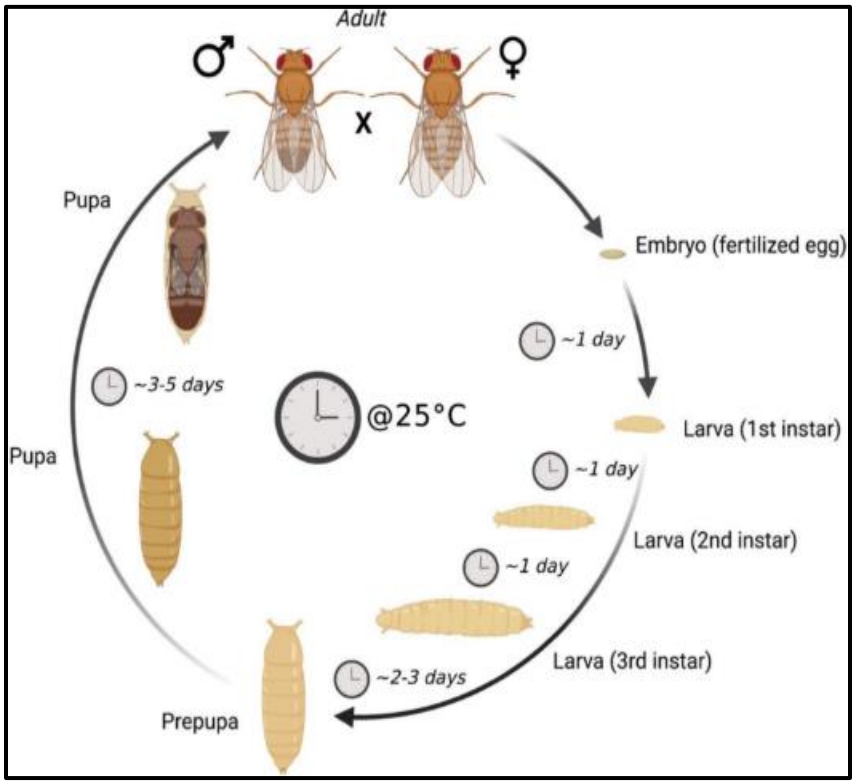

Figure 10: Life cycle of *D. melanogaster*.

I.2.5. Drosophila as a model of diabetes

Animal models have contributed immensely to the study of diabetes mellitus, providing researchers with the opportunity to examine in vivo the genetic and environmental factors influencing the development of the disease and its complications. In addition, performing functional studies in animal models helps generate reproducible data and overcome the limitations imposed by human research. Here, we focused on *Drosophila* as a model of diabetes.

Over the past twenty years, *Drosophila melanogaster* has been widely used to dissect the functional and structural components of the genome (Corradini *et al.,* 2014; Mohr et al., 2014), to study the mechanisms underlying aging (De Nobrega *et al.,* 2020) and to characterize several

human diseases, such as neurodegenerative diseases (Liguori *et al*., 2021; Specchia *et al*., 2019; Tsuda & Lim, 2018), cardiovascular (Zhu *et al*., 2017), renal (Millet-Boureima *at al.,* 2018), and metabolic, including diabetes (Graham & Pick, 2017). The use of *Drosophila* in metabolism studies became possible after the discovery that flies and humans share most metabolic pathways (Bharucha, 2009). The development of potent genetic strategies combined with multiple resources, such as gene silencing and transgenic stocks, allows functional studies to be carried out effectively, inexpensively, and efficiently. In addition, flies offer the possibility of large-scale screening to identify new genes and pathways involved in the pathophysiology of the disease, ultimately representing potential targets for drugs. Finally, flies can be used as a low-cost, time-saving screening platform in the early stages of drug development.

I.2.6. Glucose homeostasis in Drosophila

Glucose homeostasis is maintained in a remarkably preserved manner in *Drosophila*. Flies have insulin and glucagon homologues that perform the same functions as mammalian hormones. Eight genes code for insulin-like peptides (DILPs)Drosophila, designated DILP1 to DILP8. Of these proteins, DILP2, DILP3 and DILP5 are involved in the regulation of glucose levels in hemolymph and fat storage, as well as in the control of development, body size and body life longevity (Grönke *et al*., 2010 ; Nassel *et al.*,2013 ; Brogiolo *et al*., 2021).

DILPs are secreted by a group of 14 specialized cells in the brain, called insulin-producing cells (IPCs), which represent the counterpart of the mammalian endocrine pancreas. Adipokinetic hormone (AKH) is, on the contrary, the homolog of glucagon and is produced by cardiac body (*CC)* cells in the neuroendocrine ring gland (Kim and Rulifson, 2004; Lee and Park, 2004).

Drosophila has an open circulatory system, hemolymph, in which trehalose and glucose are the most abundant sugars; trehalose consists of two glucose molecules and is synthesized in the adipose body, the flying organ corresponding to the liver and adipose tissue. Trehalose levels are 100 times higher than those of glucose (Kim and Rulifson, 2004), but its hemolymph concentration is more flexibly regulated than that of glucose; perhaps because, being a non-reducing sugar, its accumulation does not produce any toxic effects. In contrast, *Drosophila*

glucose levels are tightly regulated, as in mammals (Pasco and Leopold 2012; Ugrankar *et al*., 2015).

In the brains of adult flies, DILPs are secreted by IPCs by mechanisms similar to those observed in mammals. Glucose-mediated activation of IPC involves the closure of K^+ ATP channels and the opening of Ca^{2+} channels, which triggers the release of DILPs (Fridell *et al*., 2009; Kréneisz *et al*., 2010).

The insulin signaling pathway is well conserved in flies (Inoue *et al*., 2018). Vertebrate and Drosophila insulin receptors are equivalent (Fernandez *et al*., 1995), as shown by the discovery that chimeric insulin receptors in fruit flies and vertebrates are activated with a similar mechanism (Yamaguchi *et al*., 1995). However, unlike mammals, InR is the only insulin receptor that provides both energy metabolism and growth control (Brogiolo *et al*., 2021).

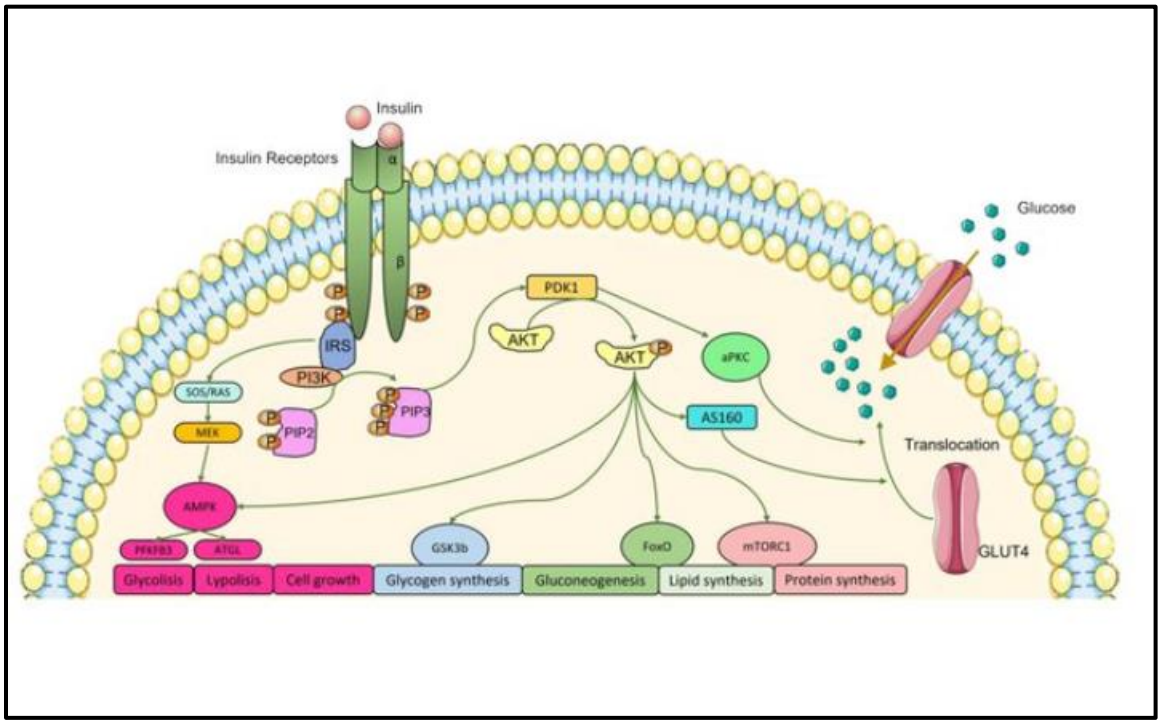

Figure 11: Schematic representation of insulin signaling pathways. When insulin binds to its receptor (IR), autophosphorylation of tyrosine kinase residues occurs and various downstream regulatory proteins are recruited. The insulin signal is transduced among the target proteins/enzymes ending with the fusion of the glucose transporter 4 (GLUT4) vesicle with the

cell plasma membrane and the placement of GLUT4 transporters in the plasma membrane leading to the uptake of glucose. IRS, insulin receptor substrate; PI3K, phosphatidylinositide-3-kinase; PIP2, phosphatidylinositol (4,5)-biphosphate; PIP3, phosphatidylinositol (3,4,5)-triphosphate; PDK1, phosphoinositide-dependent protein kinase-1; AKT, protein kinase B; AS160, Akt substrate of 160 kDa; aPKC, atypical protein kinase C; SOS/RAS, son of sevenless; MEK, mitogen-activated protein kinase; AMPK, mitogen-activated protein kinase; PFKFB3, 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3; ATGL, adipose triglyceride lipase; GSK3b, glycogen synthase kinase b; FoxO, forkhead box protein O1; mTORC1, mammalian target of rapamycin complex 1; GLUT4, glucose transporter type 4 (Capucho *et al*., 2022).

I.3. General information about the plant

The *Ficus* is one of the largest genres of Angiosperms with more than 800 species worldwide. This genus belongs to the family of the Moraceae, rich in species milky latex and Drupes or achenes aggregated as fruit. *Ficus Carica* is the most important commercial species of the genus because of its fruits, which are inflorescence closed with a hollow succulent receptacle (Mawa *et al*., 2013). This species can generate two crops per year: the main fruits, figs, which are produced in the concomitant growing year and are collected at the end of the harvest and the breba crops, which formed in the previous growing year and remain dormant during the winter producing an early harvest (Aradhya *et al*., 2010). *F. Carica* is native to the Middle East, domesticated from a group of fig trees from the Mediterranean region, associated with the grapes and trees at the beginning horticulture this region. Its history of domestication and its expansion around the world have strongly influenced its current distribution, fruit morphology and genetic diversity.

I.3.1. Origin and geographical distribution

F. carica is an important crop that most often appears on the market in its fresh or dry form, consumed directly or as part of culinary dishes. In the last ten years (data available from 2010 to 2019), Turkey, Egypt and Algeria have been the largest producers of figs in the world. According to FAOSTAT, only Spain was among the top 10 producers of figs in Europe. Consumption of this fruit has increased worldwide and is estimated to increase significantly in the coming years (Shamin-Shazwan *et al*., 2019).

I.3.1.a. Worldwide

The fig tree (*Ficus carica*) is native to the eastern Mediterranean region, where very old spontaneous fig trees can still be found today (in Turkey, Syria and Arabia). Subsequently, the cultivation of the fig tree spread to all Mediterranean countries, with a range from the Canary Islands to India and Pakistan, on the coasts of the Atlantic Ocean as well as on all those of the Mediterranean and in the Middle East (El Rayes, 1995).

I.3.1.b. In Algeria

In Algeria, fig tree cultivation is widespread throughout the country (coastal, steppe and Saharan areas) because of its pedoclimatic adaptability, its nutritional and therapeutic properties, as well as its contribution to the culinary practices of Algerians. In the mountainous region of Kabylia, fig production in Algeria is mainly concentrated (Bejaia and Tizi-Ouzou account for 27% and 13% of total national production, respectively) (MADR, 2012).

I.3.2. Taxonomic heading

The botanical classification of the fig tree is as follows: (Chawla *et al*., 2012) (Figure 12).

Plant kingdom	
Superphylum Spermatophyte	
Phylum Phanerogams	
Class Dicotyledons	
Hamamelidae subclass	
Order Urticales	
Family Moraceae	
Genus Ficus	
Species	*Ficus carica*

Figure 12: Taxonomy of *Ficus carica* (Chawla *et al*., (2012).

I.3.3. Botanical description of the fig tree

Fig, known botanically as *Ficus carica* is a generic term that means wart for *Ficus* (fig tree milk to treat wart) and carica refers to a region in Turkey. It is part of the Moraceae family, which has about 1500 species in 52 genera, including the genus Ficus described by Linnaeus (Vidaud, 1997).

It is a subtropical plant, or adapted to temperate to warm climates, but it can be grown at high altitudes (up to 1500 meters) in many tropical countries. (Leroy, 1968).

It is perceived as a tree 12 to 15 meters high that forms a robust sword. Its parts are all covered with latex, its leaves are alternate, palmate but extremely varied. The flowers are extremely unique because they are found in an inflorescence called a sycone (Bertaudeau and Faure, 1990). Latex is white and milky which is mainly composed of ficin, a hydrolytic enzyme of proteins. In general, the root system of the plant is shallow and scattered (Badgujar *et al*., 2014) (Figure 13).

This species has a remarkable ability to regenerate and produce fruit without having visible flowers. It produces two types of figs: figs from the first harvest or flowering figs (El bakkor) and figs from the second harvest or autumn figs (karmouce). Flowering figs are formed on the defoliated branches of the previous year (Twig *et al*., 2008).

Figure 13: Fruit-bearing branches of *Ficus carica* (Bakshi *et al.* 1999).

I.3.4. Chemical composition

Figs offer a rich source of minerals, vitamins and dietary fibre, being both high in fat and cholesterol-free, and containing a large number of amino acids. Like other fruits, figs are composed of sugars and organic acids that impact their quality (Mahmoudi *et al*., 2018).

- **Carbohydrates**

The qualitative study of fig carbohydrates revealed the presence of free sugars, mainly glucose and fructose, as well as a low amount of sucrose, as well as surpluses of galactose and arabinose (Golubev *et al*., 1987) and xylose (Omondi Owino *et al*., 2004). The total sugar content is between 9.8 and 18.9% when fresh (Babazadeh darazi, 2011).

- **Proteins and amino acids**

About 17 amino acids are present in it, including aspartic and glutamic acids. (Solomon *et al*., 2006) according to Lim (2012), the levels of "acidic" amino acids are higher than those of other amino acids present in figs, whether fresh or dried.

- **Lipids**

Figs contain a limited amount of fat, about 1.9%. However, even if their concentration is low, lipids play an essential role in the storage time, organoleptic characteristics and nutritional and biological value of the fig (Kolesnik *et al*., 1987).

Fig lipids are distinguished by a high rate of unsaturation (>68%) of monovalent fatty acids, most of which are polyunsaturated, which may explain the oxidative deterioration of fig and its derivatives in some cases (Kolesnik *et al*., 1987).

- **Dietary fibre**

It is a fibrous plant (Guvenc *et al*., 2009). Dietary fibre includes lignin as well as various carbohydrates such as cellulose, hemicelluloses, pectins, resistant starches, and non-digestible oligosaccharides (Ramulu and Rao, 2003).

- **Vitamins**

Figs contain a high number of water-soluble vitamins B1, B2 and C (Farahnaky *et al*., 2009). Figs also contain fat-soluble vitamins, with a predominance of vitamins E and K (Lim, 2012).

- **Minerals**

It contains significant concentrations of minerals essential for metabolism, such as P, K, Ca, Mg, Na, Fe, and Z (Mendoza-Castillo *et al*., 2019).

- **Organic acids**

Oxalic, malic, citric, shikimic and fumaric acid are organic acids that are very abundant in figs (Oliveira *et al*., 2009).

I.3.5. Extraction, separation and refinement of fig biomolecules

The use of fig and its byproducts as a food source or as pharmacological agents to improve human health dates back thousands of years. Figs are an excellent source of different biologically active biomolecules and are responsible for a wide range of bioactive effects: antioxidant, anti-inflammatory, anticancer, antimicrobial, anti-aging and Healing (Abdel-Rahman *et al*., 2021;Boyacıoğlu *et al*., 2021). The main bioactive molecules found in various products of the fig and its byproducts are terpenoids, carotenoids, Phytosterols, volatile organic compounds, phenolic acids and Flavonoids especially Anthocyanins, flavanols, flavan-3-ols and flavanones (Pereira *et al*., 2017). The presence of these metabolites with high added value and attractive applications in the food, cosmeceutical and Nutraceutical has increased the potential for the recovery of these by-products. The use of fig as a low-cost source of bioactive compounds as ingredients for new products and/or nutraceuticals, or as a feedstock for secondary processes, is highly dependent on the availability of adequate technology for the extraction of these bioactive compounds (Alexander *et al*., 2017;Bey *et al*., 2013). These vital extraction procedures, performed using several conventional extraction methodologies, including Soxhlet, maceration(M) and Hydro distillation, usually require organic, a large volume of solvents, a long Extraction time and high energy consumption (Taofiq *et al*., 2019). Some of these conventional methodologies have traditionally been applied to recover different high-value compounds from

fig by-products using solvents, such as ethanol, methanol, acetone, or Ethyl acetate, alone or in combination with water.

I.3.6. Biological properties of the Fig and its by-products

Existing studies on the pharmacological functions have revealed that the observed *Ficus* species possessed a broad range of biological properties, including antioxidants, antidiabetic, anti-inflammatory, anticancer, antitumor and antiproliferative, antimutagenic, antimicrobial, anti-helminthic, hepatoprotective, wound healing, anticoagulant, immunomodulatory activities, antistress, toxicity studies, and mosquitocidal effects.

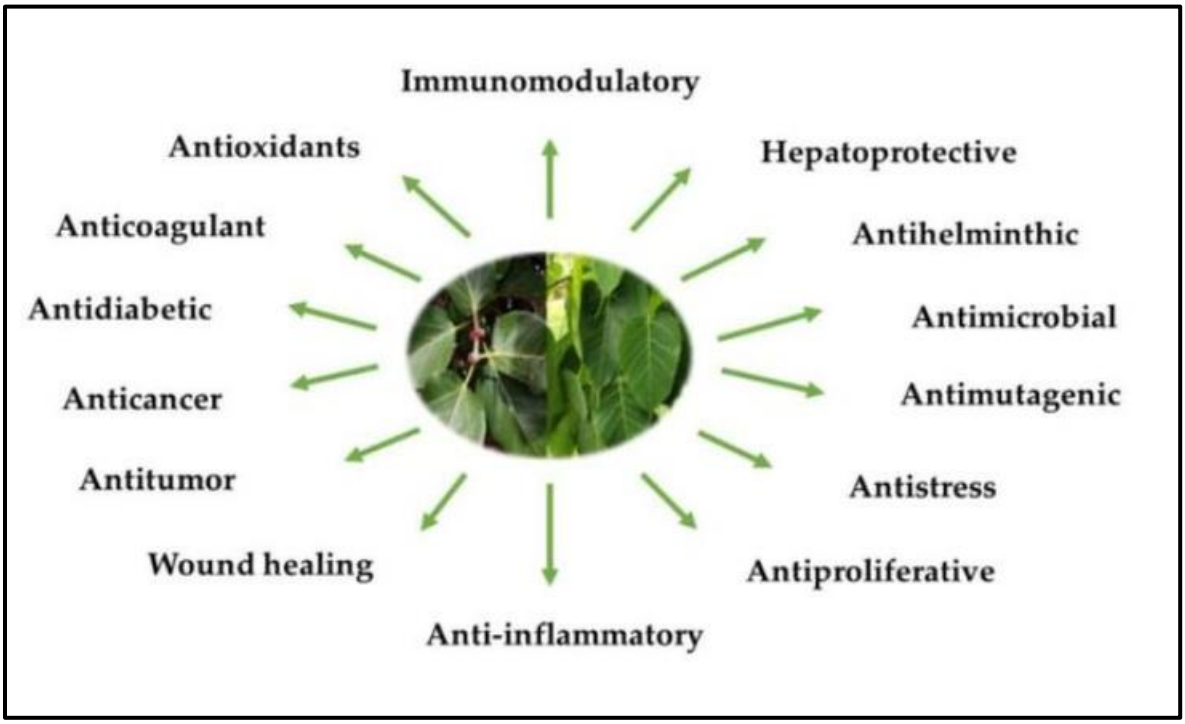

Figure 14: Pharmacological activities of *Ficus carica*.

- **Antidiabetic activity**

Nowadays, diabetes has become the most common endocrine disease. It is considered a metabolic disorder characterized by an imbalance of the Carbohydrate and lipid metabolism, giving rise to glucose levels high (Tripathy *et al*., 2021). The incidence of diabetes continues to rise, and synthetic antidiabetic drugs are the most widely used therapeutic intervention to treat the disease. There is a preference for naturally derived pharmaceutical formulations over their synthetic counter-pathways due to the minimal efficacy and safety issues associated with the latter. In this context, several plants have been shown to exert antidiabetic activity, including *Ficus Carica* is included (Deepa *et al*., 2018).

The excerpts of figs show antidiabetic activity through different mechanisms: 1) inhibition of glucose absorption in the intestinal tract via inhibition of α-glucosidase and α-amylase, 2) improvement of glucose absorption via glucose transporter type 4 (GLUT4)-phosphatidylinositol-3 kinase (PI3K)-serine/threonine-protein kinase, and 3) regulate glucose homeostasis via activation of protein kinase(AMPK) (Figure 14) (Deepa *et al*., 2018). On the other hand, they also show a close connection with antioxidant activity. One study showed that the IC50 of leaf extract was 5.50 µM (ascorbic acid = 4.8 µM). This activity has been attributed to flavonoids (quercetin, kaempférol and chrysin) and was also correlated with low levels of transaminases and protective effects in diabetic neuropathy (Khan Dureshahwar, Mohammed Mubashir *et al*., 2019). In the same perspective, oral ingestion of ficusine, a known furanocoumarin, increased the expression of Related antioxidant enzymes such as superoxide dismutase(SOD),Catalase(CAT) and glutathione peroxidase (Gpx) in the rat model (Irudayaraj *et al*., 2016,2017). In general, most studies on the antidiabetic activity of extracts of *Ficus carica*. Were conducted in leaves (Deepa *et al*., 2018) (Table 02).

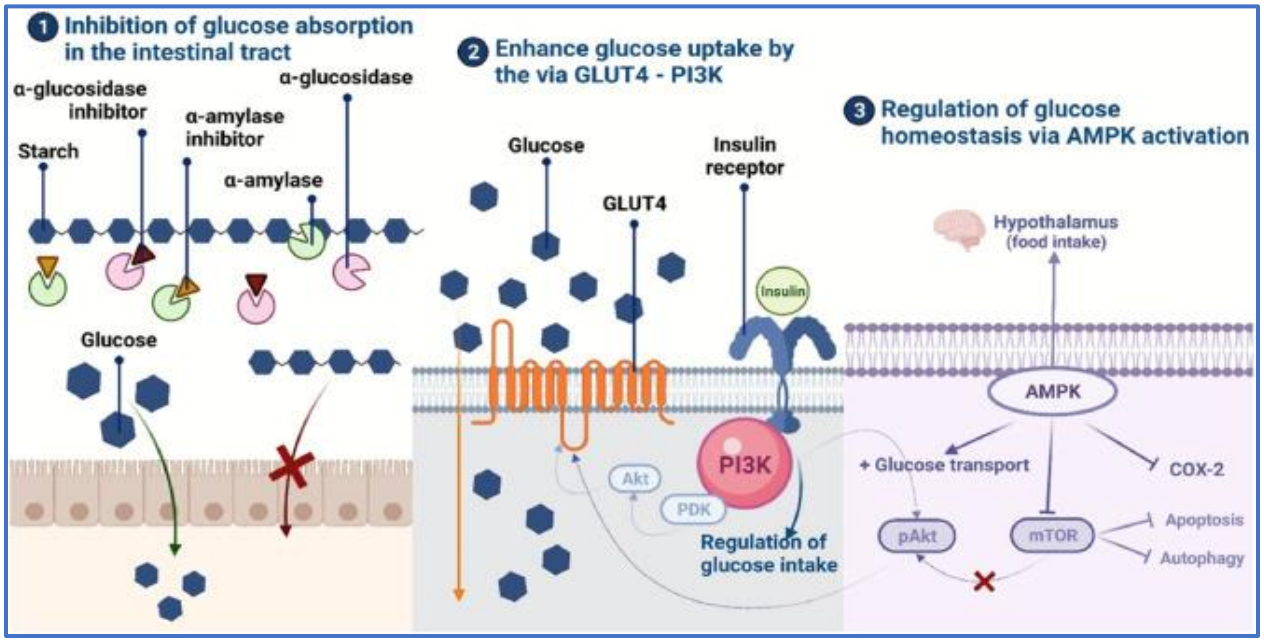

Figure 15: Mechanism of action of fig extracts antidiabetic activity.

By-product	Compound	Test	Dose	Results	Ref
Antidiabetic activity					
Leaves	Ficusine	Diabetic rats in vivo: FBG levels, body weight, PI level, TC, TG, HG, carbohydrate-metabolizing enzymes	250 and 500 mg/kg	Decreased levels of FBG and PI, BW, TC, TG, HG, PI, enzymes	Irudayaraj *et al*., 2017)
Leaves	Ficusine	Diabetic rats in vivo: body weight, IP, HG, TC, TG, FFA, liver markers	20 and 40 mg/kg	Decreased levels of PI, BW, AST, ALP, ALP, HG, TC, TG, FFA	(Irudayaraj *et al*., 2016)
Leaves	Sd	HepG2: MTT, WB, q-PCR (Hepatic	–	IC50 = 82.29 µg/mL. Reduced expression	(Zhang *et al*., 2019)

		Gluconeogenic Enzymes)		levels via AMPK.	
		Diabetic mice in vivo: FBG levels, IP levels, TCs, TGs,	1000mg/kg	Decreased levels of FBG and TG. No effect on TC, PI levels	
Leaves	Quercetin, kaempferol and chrysin	Diabetic rats in vivo: BGL and neuropathy, hepatic and renal markers	25 to 100 mg/kg	Reduction of BGL. Increased expression of PWL and SGOT, SGPT, BUN	(Khan Dureshahwar, Mohammed Mubashir *et al*., 2019)

Table 02: Biological properties of the fig and its by-products.

Materials and Methods

II.1. Laboratory breeding

Drosophila have been reared in the laboratory since the beginning of the twentieth century, following the pioneering work of Sturtevant (1913) who established the first genetic mapping. This species is currently used as a biological model in genetics, molecular biology and toxicology by 80,000 to 100,000 researchers (Colombani *et al*., 2006).

The breeding of *D. melanogaster*, Canton S strain, is carried out, in the laboratory (Figure 15), at a temperature of 25°C, a humidity of 70% and a scotophase of 12 h (strain donated free of charge by C. Wickers Thomas, Evolution, Genomes and Speciation Laboratory, University of Paris Sud).

The agar artificial nutrient medium on which Drosophila is bred is based on corn flour and brewer's yeast. It is essentially composed of

- Corn flour: 33.3 g
- Dry yeast: 33.3g
- Agar-agar: 4.8 g
- 10% methyl hydroxybenzoyate antifungal
- Distilled water: as required

Fruit flies are raised in plastic vials and capped with a foam buffer (Figure 15).

The flies are transferred every 3-4 days to new tubes in order to avoid problems with larval competition and provide sufficient offspring.

Figure 16: Laboratory rearing of *D. melanogaster* (personal photo).

II.2. Processing

II.2.1. Preparation of the plant

Our study focuses on the *Ficus carica* plant, harvested in the region (Skikda) in February 2025. Only the leaves of the plant were used in this study.

The *Ficus carica* plant was picked and washed to remove all traces of dust and impurities. It is dried in an oven at 40 °C for 10 days. Once completely dried, the *Ficus carica* plant was ground using an electric grinder and then sieved to become a fine, homogeneous powder. The resulting powder was stored in a glass container and stored away from light and moisture.

Figure 17: The powder of F. *carica* leaves.

II.2.2. Collection and grouping of larvae

The five-day-old female flies were quickly transferred to vials containing a fresh basal diet. Adult flies were removed after laying eggs for a period of 12 hours, and then the first instar (L2) larvae were collected the next day and used for this experiment due to their higher feeding rate, rapid development, and sexual immaturity compared to adults. Diabetic-like phenotypes were induced in larvae using a sucrose-rich diet (30% w/v).

The larvae were divided into groups of 20 larvae per box. Group 01 was subjected to a normal diet while groups 02 to 05 were subjected to a normal diet with other variables described below;

Groups - Treatment

Group 01: standard food medium + 2% sucrose.

Group 02: food medium + 30% sucrose.

Group 03: food medium + 30% sucrose + 2.5% *Ficus carica*.

Group 04: food medium + 30% sucrose + 0.5% metformin.

Group 05: food medium + 30% sucrose + 2.5% *Ficus carica* + 0.5% metformin.

II.2.3. Food consumption tests (MultiCAFE: Multi Capillary Feeding)

To estimate the amount of liquid consumed, a MultiCAFE (multiple capillary feeding) assay was performed on adult flies reared under different dietary conditions: standard diet (control), 30% sucrose-enriched diet (Suc30%), Suc30% + *Ficus carica*, Suc30% + metformin, and Suc30% + *Ficus carica* + metformin. Three-day-old males and females were separated by sex and placed individually in tubes containing moistened cotton for 20 to 22 hours to induce mild food deprivation.

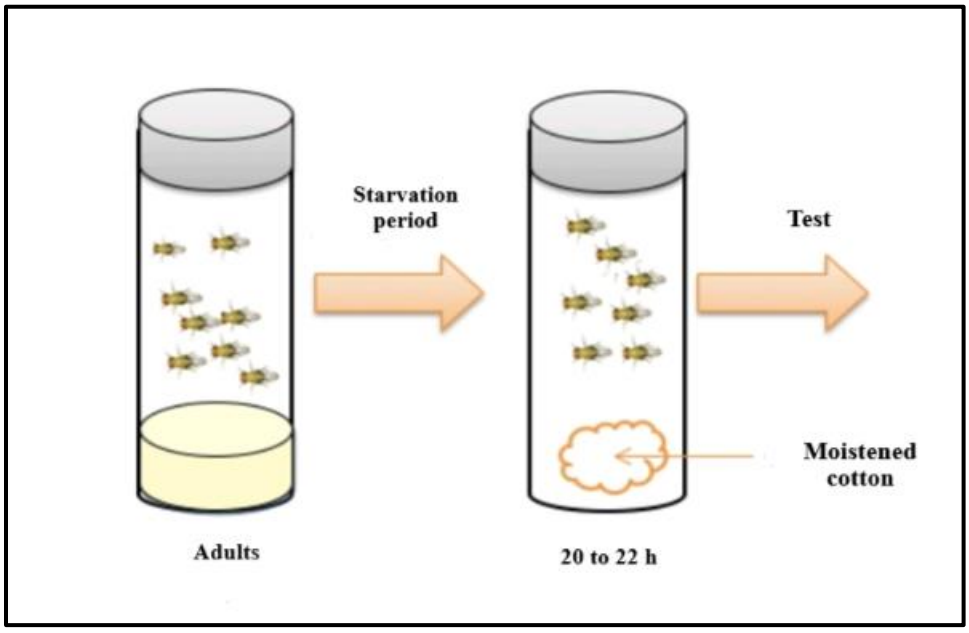

Figure 18: Scheme representing the preparation of mouthpieces for the MultiCAFE test.

After this pre-treatment, flies were transferred to individual rectangular cages, each equipped with two 5 µL capillaries (Hirschman, VWR) filled with test solution. Each set of 10 individual cages was placed in a sealed box, which also included two empty cages (without flies) used to measure evaporation. A moistened paper filter was added to maintain high humidity levels throughout the assay. The boxes were kept at 25 °C, and a Logitech HC920 webcam was used to capture one image per minute over a two-hour period.

At the end of the experiment, images were analyzed using a Java-based plugin developed by Prof. F. Marion-Poll, running on the ICY image analysis software (Chaumont et al., 2012), in order to quantify the volume of liquid consumed and correct for evaporation. The tested solutions included 30 mM sucrose alone or combined with 10 mM caffeine (CAF) to enhance attractiveness. All solutions were colored with Brilliant Blue to facilitate consumption quantification. Each experimental condition was replicated five times for each dietary group.

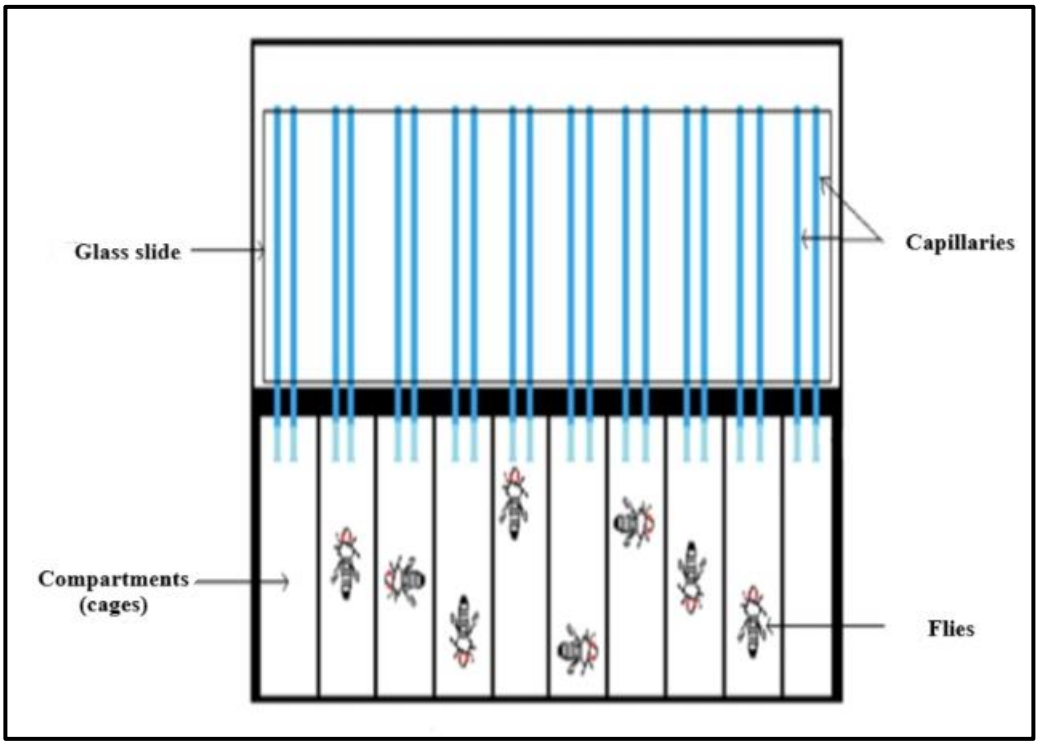

Figure 19: Scheme of the device for the multiple-choice dietary test (MultiCAFE).

II.2.4. Starvation sensitivity

For the starvation resistance assay, 4- to 5-day-old flies from each dietary group (standard diet, Suc30%, Suc30% + *Ficus carica*, Suc30% + metformin, and Suc30% + *Ficus carica* + metformin) were placed in vials containing 1% agar, which served as a moisture source without nutritional content. All vials were incubated under constant conditions (25 °C, 12 h/12 h light/dark cycle, 65% relative humidity). Dead flies were recorded every 2 hours until all individuals had died.

II.3. Statistical analysis

Data are expressed as means ± standard error of the mean (SEM) for each experimental group. Homogeneity of variances was verified using Bartlett's and Brown–Forsythe tests. One-way and two-way analyses of variance (ANOVA), followed by Tukey's Honest Significant Difference (HSD) post hoc test, were applied to assess differences in food consumption assays. For the starvation resistance assay, survival data were analyzed using the Kaplan–Meier method, and statistical significance was determined using the log-rank (Mantel–Cox) test. All statistical analyses were performed using GraphPad Prism version 6.1 for Windows (GraphPad Software, La Jolla, CA, USA; www.graphpad.com).

Results and Discussion

III.1. Results

III.1. Effects of *F. carica* and metformin on the food consumption

Exposure of larvae at the early L2 stage to a high-sucrose diet containing 30% sucrose (Suc30%) resulted in a significant increase in food consumption in adult males compared to the control group ($p < 0.0001$). The mean consumption values for males were 3.30 ± 0.035 µL/fly in the Suc30% group versus 2.10 ± 0.035 µL/fly in the control group, corresponding to an approximate 57% increase (Fig. 20 A, Table 03).

The addition of *Ficus carica* or metformin to the Suc30% diet reduced consumption in males compared to the Suc30% group alone, with mean values of 2.67 ± 0.012 µL/fly for Suc30% + F. carica, 2.27 ± 0.026 µL/fly for Suc30% + metformin, and 2.52 ± 0.026 µL/fly for the combined Suc30% + *F. carica* + metformin group. These reductions were significant, suggesting a moderating effect of the treatments on the overconsumption induced by the high-sucrose diet.

In female the exposure of larvae at the early L2 stage to a high-sucrose diet containing 30% sucrose (Suc30%) led to a significant increase in food consumption in adults compared to the control group ($p < 0.0001$). The average consumption was 3.62 ± 0.053 µL/fly for the Suc30% group, compared to 2.77 ± 0.028 µL/fly for the control group, representing an increase of approximately 31% relative to the control (Fig. 20 B, Table 04).

Treatment with *Ficus carica* and metformin, alone or in combination, significantly reduced food consumption compared to the Suc30% group. The average consumption values were 3.16 ± 0.017 µL/fly for Suc30% + *Ficus carica*, 3.35 ± 0.019 µL/fly for Suc30% + metformin, and 2.97 ± 0.049 µL/fly for Suc30% + *Ficus carica* + metformin. All these reductions were statistically significant ($p < 0.001$).

These results suggest that a high-sucrose diet induces a significant increase in food consumption in both sexes, reflecting hyperphagia related to metabolic stress. This hyperphagia is significantly reduced by treatments with Ficus carica and metformin, alone or in combination, indicating a potential regulatory role of these agents in modulating food intake under conditions of excessive sugar intake.

Table 03: Effects of *F. carica* and metformin, on food consumption following a high-sucrose diet administered during the early L2 larval stage of *Drosophila melanogaster* Male, (m ± SEM, n= 05). Analysis of variance to a classification criterion.

Source of variation	SCE	Ddl	CM	Fobs	P
Treatment	4,281	4	1,070	271,0	0.001
Residual error	0,07900	20	0,003950		
Total	4,360	24			

Highly significant difference (p< 0.001). SCE: sum of the squares of the deviations; DDL: degree of freedom; CM: medium square; Fobs: F observed; p: level of significance.

Table 04: Effects of *F. carica* and metformin, on food consumption following a high-sucrose diet administered during the early L2 larval stage of *Drosophila melanogaster* Female, (m ±

Source of variation	SCE	Ddl	CM	Fobs	P
Treatment	2,180	4	0,5449	82,72	0.001
Residual error	0,1325	20	0,006624		
Total	2,312	24			

SEM, n= 05). Analysis of variance to a classification criterion.

Highly significant difference (p< 0.001). SCE: sum of the squares of the deviations; DDL: degree of freedom; CM: medium square; Fobs: F observed; p: level of significance.

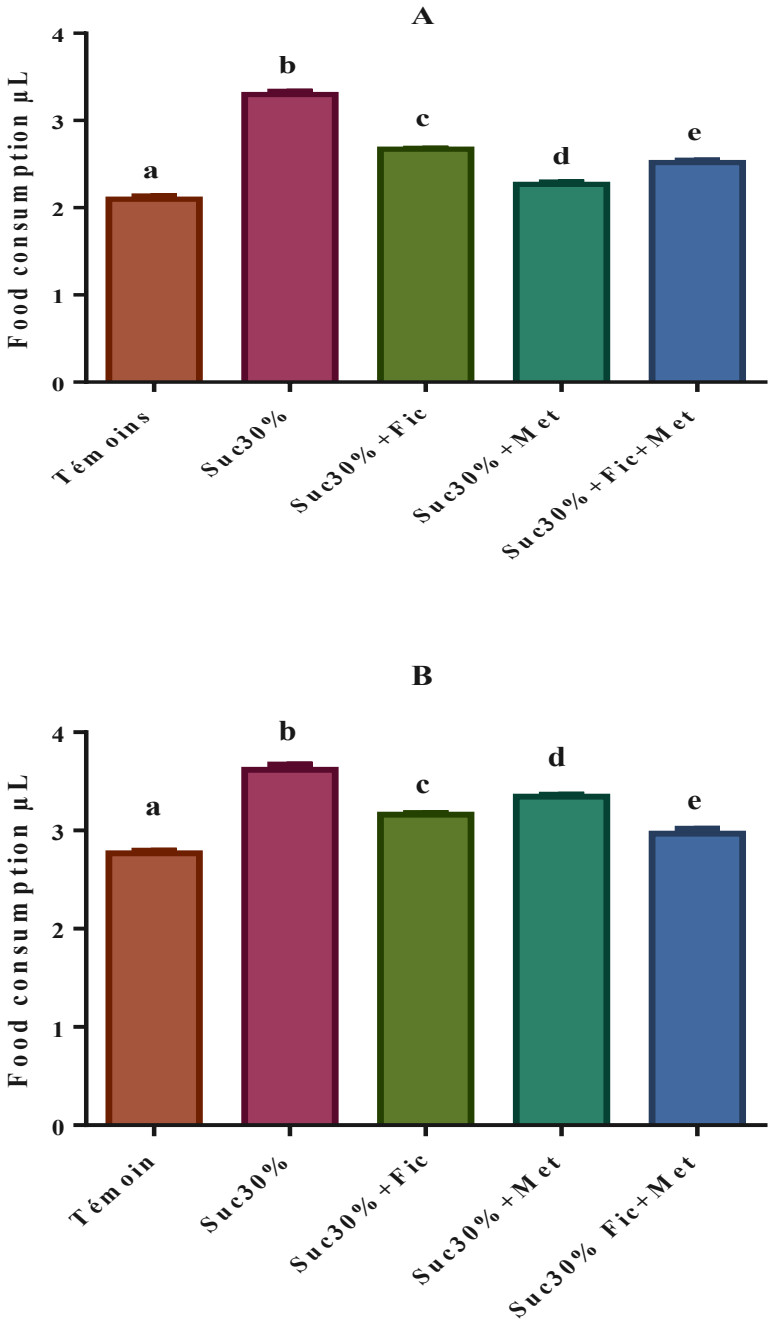

Figure 20: Effects of *Ficus carica* and metformin on food consumption following a high-sucrose diet administered during the early L2 larval stage of *Drosophila melanogaster* (mean ± SEM, n = 5). (A) Males; (B) Females. Means sharing the same letter are not significantly different ($p > 0.05$).

III.2. Effects of *F. carica* and metformin in starvation resistant adult *Drosophila*

In males, exposure of larvae at the early L2 stage to a high-sucrose diet (30%, Suc30%) led to a significant reduction in starvation resistance in adults. Overall survival curve analysis using the Log-rank test showed a statistically significant difference between groups ($\chi^2 = 9.547$; df = 4; p = 0.0488). The median survival time decreased from 42 hours in the control group (Suc2%) to 26 hours in the Suc30% group, representing a 38% reduction (Fig 20 A).

Treatment with *Ficus carica* fully restored starvation resistance, with a median survival time of 42 hours in the Suc30% + *Ficus* group. Similarly, metformin partially attenuated this decline, increasing median survival time to 36 hours in the Suc30% + metformin group.

The combined treatment exceeded the control, with a median survival time of 46 hours in the Suc30% + *Ficus* + metformin group. However, complementary tests (Log-rank test for trend, p = 0.5049; Gehan-Breslow-Wilcoxon test, p = 1.000) did not reveal a significant trend or marked differences throughout the duration, suggesting that the treatment effects vary across different phases of starvation.

In females, exposure to a high-sucrose diet (30% sucrose, Suc30%) during the early L2 larval stage significantly reduced starvation resistance in adults (Fig 20 B). Survival analysis revealed a significant difference in survival curves between the experimental groups (Log-rank test: $\chi^2 = 11.03$, df = 4, $p = 0.0262$), indicating that the dietary interventions had distinct effects on survival under starvation. However, no significant trend was observed across groups (Log-rank test for trend: $\chi^2 = 0.08086$, $p = 0.7761$), and the Gehan-Breslow-Wilcoxon test did not confirm the difference ($\chi^2 = 0.002166$, $p = 1.0000$).

The median survival time decreased from 42 h in the control group (Suc2%) to 26 h in the Suc30% group, representing a 38% reduction. Treatment with *Ficus carica* (Suc30% + fic) and metformin (Suc30% + met) mitigated this decline, increasing median survival to 42 h and 36 h, respectively. The combined treatment (Suc30% + fic + met) further improved survival, reaching a median of 46 h (+77% compared to Suc30%). These results suggest that *Ficus carica* and metformin can partially restore starvation resistance compromised by a high-sucrose diet in females, although the protective effect appears more variable than in males.

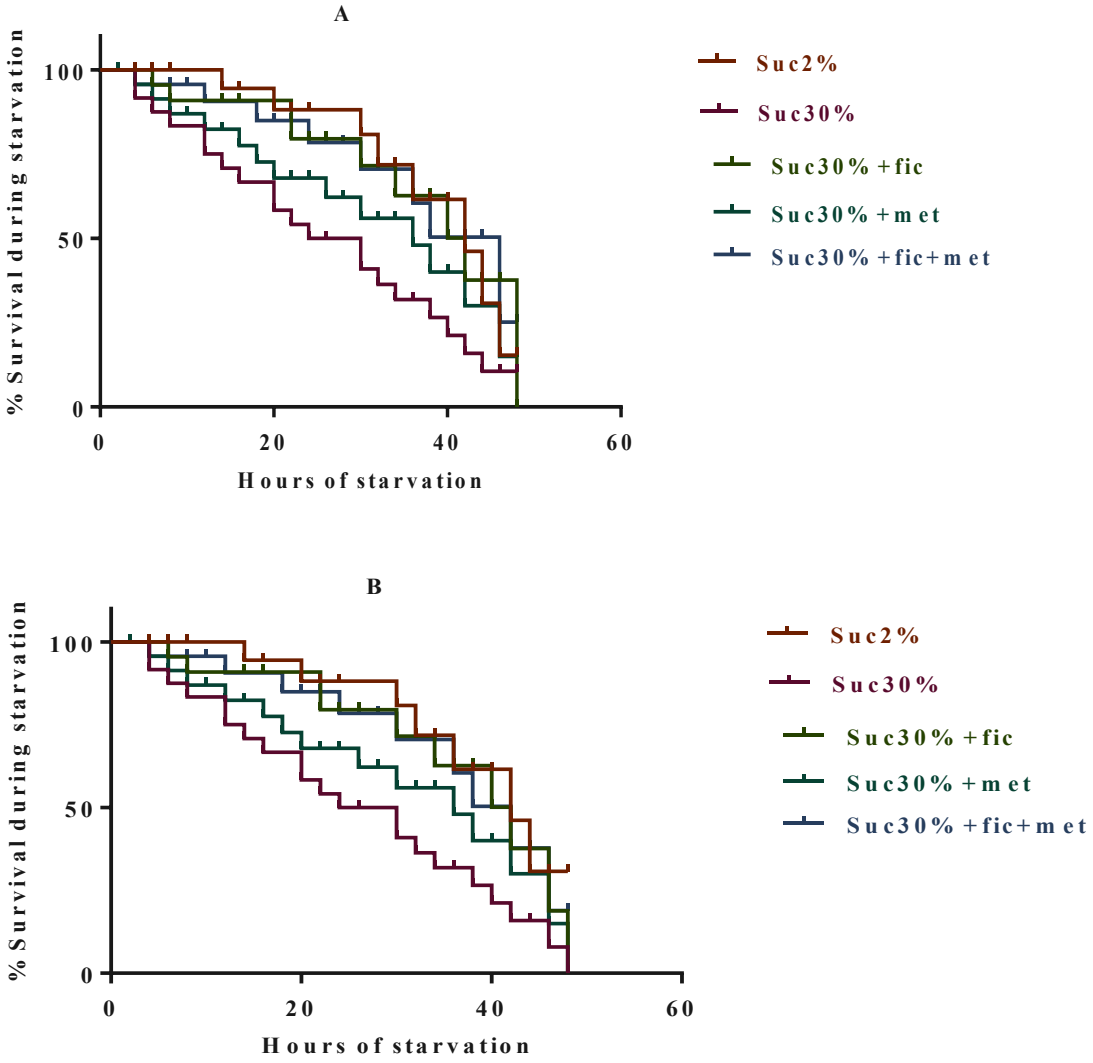

Figure 20: Effects of Ficus carica and metformin on starvation resistant following a high-sucrose diet administered during the early L2 larval stage of Drosophila melanogaster (mean ± SEM, n = 5). (A) Males; (B) Females. Means sharing the same letter are not significantly different ($p > 0.05$).

III.2. Discussion

The global increase in metabolic diseases, particularly type 2 diabetes (T2D), has renewed interest in studying the interactions between nutrition and metabolic regulation. *Drosophila melanogaster* has proven to be a relevant model for studying metabolic dysfunctions induced by high-sugar diets, due to the conservation of signaling pathways, notably the insulin pathway (Bharucha, 2009; Musselman *et al*., 2011; Rovenko *et al*., 2015).

In our study, exposing adult *D. melanogaster* to a high sucrose diet (30%) led to a significant increase in food intake as well as an alteration in fasting resistance, two parameters indicative of energy imbalance and metabolic stress (Smith *et al*., 2020; Wang *et al*., 2021). This overconsumption reflects compensatory hyperphagia, often observed in response to insulin resistance, where normal satiety regulation is disrupted (Jones *et al*., 2019).

Behavioral analysis also revealed that flies subjected to this sugary diet exhibited a decreased ability to endure a period of food deprivation, reflecting impaired management of energy reserves (Garcia *et al*., 2023). These changes are consistent with fasting intolerance models observed in other biological systems affected by nutritional excess and metabolic dysfunction.

The metabolic alterations induced by a high sucrose diet, manifested by overconsumption and reduced fasting resistance, mainly result from a disruption of insulin-like peptide (DILPs) signaling. These peptides play a central role in regulating energy homeostasis, particularly by modulating nutrient absorption and storage (Grönke *et al.*, 2010).

Insulin resistance caused by excess sucrose compromises the flies' ability to efficiently mobilize their energy reserves during food deprivation periods (Havula & Hietakangas, 2012). This deficit in energy regulation translates into an inability to maintain essential physiological functions during fasting, increasing vulnerability to metabolic stress.

Furthermore, oxidative and inflammatory stresses associated with this metabolic imbalance contribute to worsening dysfunction of metabolic signaling pathways, thereby reinforcing the vicious cycle of insulin resistance and energy disorders (Zhang *et al*., 2020; Ismael *et al*., 2022).

Thus, the combination of these mechanisms explains the reduced fasting resistance observed in flies subjected to the sugary diet, consistent with the previously described increase in food consumption.

Following these metabolic alterations, several studies have shown that excessive consumption of simple sugars leads to a profound imbalance in carbohydrate and lipid homeostasis in *Drosophila melanogaster*. Our experimental observations support these findings: flies fed a high-sucrose diet exhibited a marked increase in food intake accompanied by a significant decrease in fasting resistance. These results reflect an energy metabolism dysregulation characteristic of insulin resistance states.

This pathophysiological profile is notably explained by the abnormal accumulation of circulating sugars (glucose, trehalose) and neutral lipids such as triacylglycerols (TAG), as documented in several recent studies (Pasco & Leopold, 2012; Landayan *et al*., 2022). In insulin resistance, mobilization of energy reserves becomes inefficient, compromising survival under fasting conditions and excessively stimulating food-seeking behavior.

In this context, the organism enters a vicious cycle: persistent hyperglycemia promotes systemic inflammation and oxidative stress, two processes that exacerbate dysregulation of central metabolic pathways (Havula & Hietakangas, 2021; Arking, 2022). Although simplified, this model of metabolic dysfunction faithfully reflects some characteristics of type 2 diabetes in mammals, confirming the robustness of *D. melanogaster* as a tool to study nutritional disorders related to excessive dietary sugars.

Several recent works have highlighted the therapeutic potential of *Ficus carica* (fig tree) in regulating carbohydrate metabolism, due to its richness in bioactive compounds such as flavonoids, phenolic acids, and coumarins. These molecules are recognized for their antioxidant, anti-inflammatory, and antidiabetic properties (Paciolla *et al*., 2020; Yilmaz *et al*., 2023).

In *Drosophila melanogaster*, administration of *F. carica* extracts to flies on a high sucrose diet led to a notable improvement in food intake and fasting tolerance. Our results show a significant reduction in hyperphagia and an improvement in fasting resistance, suggesting partial restoration of energy homeostasis.

This beneficial effect could be explained by a positive modulation of insulin signaling and a decrease in systemic oxidative stress. By normalizing metabolic pathways altered by excess sucrose, *F. carica* thus helps restore the balance between energy intake and needs, which could also prevent the onset of functional obesity or advanced insulin resistance (Sohail *et al*., 2021; Rana *et al*., 2022).

Similarly to *Ficus carica*, metformin, a widely used oral antidiabetic drug, has shown beneficial effects on energy metabolism in *Drosophila melanogaster* exposed to a high sucrose diet. Its mechanism of action mainly involves activation of the AMPK pathway, which restores insulin sensitivity, reduces triglyceride synthesis, and improves fatty acid oxidation (Slack *et al*., 2012; Li *et al*., 2021).

In our study, treatment with metformin significantly corrected the feeding anomalies observed in flies exposed to excess sugar. A decrease in hyperphagia and better fasting tolerance were observed, reflecting a rebalancing of energy homeostasis.

These effects may result not only from improved peripheral insulin signaling but also from central modulation of neuronal circuits involved in food intake regulation. Additionally, the reduction of systemic oxidative stress induced by metformin could contribute to stabilizing energy reserves and improving response to prolonged deprivation (Zhou *et al*., 2023; Silva *et al*., 2020).

Mechanistically, the improvement in food intake and fasting resistance observed after combined treatment with *Ficus carica* and metformin appears to result from synergistic regulation of key metabolic pathways involved in energy homeostasis. This combination enabled more effective normalization of insulin signaling, accompanied by a marked reduction in systemic oxidative stress, two parameters strongly disturbed under high-sucrose diet conditions.

Ficus carica extract, rich in natural antioxidants, activates the Nrf2/Keap1 pathway, thereby increasing the activity of antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx), limiting cellular damage induced by reactive oxygen species (ROS) (El Ghouizi *et al*., 2023). Meanwhile, metformin enhances insulin sensitivity via AMPK activation and gluconeogenesis inhibition, reducing excessive energy demand and improving adaptation to food deprivation (Slack *et al*., 2012; Li *et al*., 2021).

Our observations suggest that the association of these two treatments efficiently restores food intake regulation capacities and increases fasting resistance, reflecting an overall improvement of energy balance in *Drosophila melanogaster* under metabolic stress.

In *Drosophila melanogaster*, food intake is a key behavioral parameter closely linked to the organism's metabolic state. It is well established that a high-sucrose diet disrupts central appetite regulation mechanisms, notably through impaired insulin and TOR signaling, which can paradoxically lead to increased consumption despite hyperglycemia (Garlapow *et al*., 2015; Tennessen & Thummel, 2011). Our results show that flies exposed to a 30% sucrose diet exhibit marked hyperphagia, confirming a disorganization of neuroendocrine circuits controlling satiety. This behavior may be attributed to decreased insulin sensitivity and altered signaling of neuropeptides such as sNPF, the functional homolog of vertebrate NPY, involved in food intake regulation (Wu *et al*., 2005; Cognigni *et al*., 2011).

Simultaneously, fasting resistance, which reflects mobilizable energy reserves, is strongly reduced in flies fed a sugary diet. This increased sensitivity to nutritional stress indicates early depletion of lipid and glycogen stores, often observed in insulin resistance models (Alfa & Kim, 2016). Treatment with *Ficus carica* leaf extract significantly reduced excessive food intake and notably improved fasting resistance. These beneficial effects may be linked to the presence of flavonoids and phenolic acids capable of regulating central metabolic signaling, restoring energy homeostasis, and limiting hypothalamic inflammation (Paciolla *et al*., 2020; Yilmaz *et al*., 2023). The corrective effect observed suggests a modulatory role of *F. carica* compounds on appetite and energy metabolism control pathways in the fly, reinforcing the therapeutic interest of this plant in metabolic disorders.

The corrective effect of metformin on fasting resistance appears to be explained by AMPK activation (AMP-activated protein kinase), a key enzyme in cellular energy metabolism regulation. AMPK activation promotes fatty acid oxidation and improves mitochondrial function, contributing to better energy endurance and efficient management of metabolic reserves during fasting (Slack *et al*., 2012; Zhou *et al*., 2023). Additionally, metformin positively modulates insulin signaling and reduces triglyceride accumulation in tissues, facilitating better nutrient utilization (Li *et al*., 2021).

Ficus carica extract contains antioxidant and anti-inflammatory compounds that improve metabolic sensitivity and limit oxidative stress related to a high-sucrose diet. These combined effects promote more balanced food intake and better fasting resistance by optimizing energy use and preserving mitochondrial function (Paciolla *et al.,* 2020; Yilmaz *et al.,* 2023). Thus, the combination of these two treatments offers a complementary approach to restore energy homeostasis disrupted by a high-sucrose diet.

Conclusion and perspectives

Our experiments were conducted on *Drosophila melanogaster* at the L3 larval stage to evaluate the antidiabetic effects of *Ficus carica* extract and metformin, focusing specifically on food consumption and starvation resistance in adults subjected to a high-sucrose diet (30%). The results showed that this diet induced a significant increase in food intake along with a marked decrease in starvation resistance, reflecting an energy imbalance and metabolic dysfunction.

Treatment with *Ficus carica* extract and metformin led to a notable improvement in both parameters, with a significant reduction in hyperphagia and enhanced tolerance to food deprivation, suggesting a partial restoration of energy homeostasis. These effects may be explained by a positive modulation of insulin signaling and a reduction of systemic oxidative stress, thereby helping to correct metabolic dysfunctions induced by the high-sucrose diet.

These findings confirm the therapeutic potential of *Ficus carica* extract in mitigating metabolic disorders related to type 2 diabetes, particularly regarding the regulation of feeding behavior and resistance to nutritional stress. The use of *Drosophila melanogaster* as a biological model proved relevant for studying the systemic effects of a high-sucrose diet and plant-based treatments.

Future studies could be complemented by:

- Assessing the impact of treatments on other metabolism-related behaviors, such as locomotor activity or oxidative stress response;
- Investigating potential interactions between bioactive compounds in *Ficus carica* extract and cellular metabolic pathways using transcriptomic or proteomic approaches;
- Exploring the effects of these treatments in more complex animal models to validate the translational relevance of the results;
- Developing optimized formulations combining *Ficus carica* extract and metformin to maximize therapeutic efficacy while minimizing side effects.

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