HOW SIMILAR ARE YOU TO THE FRUIT FLY? *DROSOPHILA MELANOGASTER* AS MODEL FOR STUDYING HUMAN DISEASES

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ABSTRACT

Drosophila melanogaster is a holometabolous insect with a short life cycle. Its genome is completely sequenced, and it is easy to grow in the laboratory. More than 120 years of history using *Drosophila* have allowed us to clarify the inheritance laws and to understand cellular and molecular mechanisms of mammalian development in this model. Approximately 75% of the genes responsible for several human diseases have homologs in the fruit fly. This work addresses some advantages of using this model organism for human pathophysiology studies. Neurodegenerative disorders, heart disease, and nephropathies can be modeled in transgenic organisms, affecting the homologous gene or expressing the human sequences. It is also possible to study multi-organ pathophysiological conditions such as aging, diabetes, and cancer. In addition, *Drosophila* has been used to explore substances of human consumption such as cocaine, methamphetamine, caffeine, alcohol, tobacco, and cannabinoids. Finally, the versatility of this organism and the knowledge of its genome have made it possible to undertake large-scale pharmacological studies to learn about the interactions between substances and genes, to find new drugs.

Keywords: *Drosophila*, diseases, drugs, modeling, pharmacogenomics

RESUMEN

Drosophila melanogaster es un insecto holometábolo que presenta un ciclo de vida corto; su genoma está completamente secuenciado y es muy fácil de criar en el laboratorio. Más de 120 años de historia utilizando a *Drosophila* han permitido clarificar las leyes de la herencia y entender algunos mecanismos celulares y moleculares del desarrollo del mamífero en este modelo. Aproximadamente el 75% de los genes responsables de ciertas patologías humanas tienen homólogos en la mosca de la fruta. Este trabajo aborda algunas de las ventajas de utilizar a *Drosophila melanogaster* como organismo modelo para estudiar la fisiopatología humana. Con el uso de organismos transgénicos que tienen afectado uno o más genes homólogos, o que expresan genes humanos, se pueden modelar diferentes enfermedades neurodegenerativas, cardiopatías y nefropatías. También es posible ahondar en el estudio de condiciones fisiopatológicas multiorgánicas como por ejemplo el envejecimiento, la diabetes y el cáncer. Además, se ha utilizado a *Drosophila* para estudiar sustancias de consumo humano tales como cocaína, metanfetamina, cafeína, alcohol, tabaco y cannabinoides. Finalmente, la versatilidad de este organismo y el conocimiento de su genoma han permitido abordar estudios farmacológicos a gran escala, para conocer las interacciones entre las sustancias y los genes, con el objetivo de diseñar nuevos fármacos.

Palabras claves: *Drosophila*, enfermedades, drogas, modelo, farmacogenómica

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Characteristics of the Fruit Fly

The fruit fly *Drosophila melanogaster* (Diptera: *Drosophilidae*) is a small holometabolous insect because its development consists of a complete metamorphosis through four stages: egg, larva, pupa, and adult. Adult individuals are about 3 mm long. Their bodies are brown with black stripes and their eyes are red. However, due to several genetic mutations, there are individuals with different eye and body colors. In nature, *Drosophila* feeds on fruit and other decaying items rich in sugar. The life cycle from oviposition to adults is relatively short and lasts about 10-12 days at 25°C. Females lay up to 100 eggs per day throughout their lives at room temperature. Adults live around 70 days or more, but both survival and fertility are modified according to temperature [1].

Looking to the past: remarkable experiments with the fruit fly

By 1901, scientists William Castle at Harvard University, Frank Lutz at Cold Spring Harbor, and Fernandus Payne at Indiana University were already using the fruit fly in their research. It was Castle's publications that sparked the interest of several laboratories in *Drosophila* as an organism for genetic and evolutionary studies [2].

In 1910, Thomas Hunt Morgan, an American biologist, identified for the first time a white-eyed mutant male. Through successive crosses, Morgan concluded that the inheritance of certain traits was sex-linked. Further experiments in his laboratory provided evidence supporting Walter Sutton and Theodor Boveri's chromosomal theory of inheritance. This theory highlights that the factors responsible for inheritance (genes) are found in chromosomes and that the behavior of chromosomes during meiosis could explain the laws of inheritance described by Gregor Mendel [2,3].

Morgan's discoveries through his research with the fruit fly allowed him to win the Nobel Prize in 1933. Five other Nobel prizes were awarded to scientists who developed their experiments with *Drosophila melanogaster*: Hermann Joseph Muller (1946), Edward B Lewis, Christiane Nüsslein-Volhard, Eric F Wieschaus (1995), Richard Axel (2004), Jules A Hoffmann (2011) Jeffrey C Hall, Michael Rosbash and Michael W Young (2017). They elucidated the laws of inheritance, the generation of mutations, aspects of embryogenesis, the development of the olfactory system, the activation of the immune system, and the molecular mechanisms that control circadian rhythms, *i.e.,* the internal biological clocks of organisms, through assays in *Drosophila* [4]. Thus, in addition to becoming the exemplary model for genetic studies, *Drosophila melanogaster* became important for studies on pathophysiology in multiple areas of biomedical sciences.

Why *Drosophila* is a useful model in biology?

Drosophila melanogaster can be grown in the laboratory, easily. It is possible to raise hundreds of individuals in vials, occupying a small space and with a low maintenance cost. Their diet can be sustained by simple sources of carbohydrates (cornmeal) and protein (yeast extract). The food must be changed regularly every 10-14 days at 25°C or every 5 weeks at 18°C. The life cycle is short, so it is possible to work with successive generations in a shorter time compared to mammals [4].

The genome, transcriptome, and proteome of *Drosophila melanogaster* are characterized [5–7]. Sixty percent of its genome shows homology to the human, but unlike the human genome, it is less redundant, *i.e.*, it has fewer duplicated genes. In addition, about 75% of the genes responsible for human diseases have homologs in the fruit fly [8].

The possibility of modifying the genome and generating transgenic organisms has made it feasible to mutate fly genes and reproduce symptoms of human diseases such as Alzheimer's, Parkinson's, Friedrich's ataxia, heart disease, metabolism, among others. It has also allowed the insertion of fluorescent proteins as markers and has made it possible to regulate gene expression over time or in response to stimuli [4,9]. On the other hand, several public repositories provide numerous lines to be used by different laboratories in the world. Figure 1, shows the general aspect of a wild type fly (Top panel) and the recognizing of structures and molecular mediators mediating transgenic approaches inserting reporter system (Bottom panel).

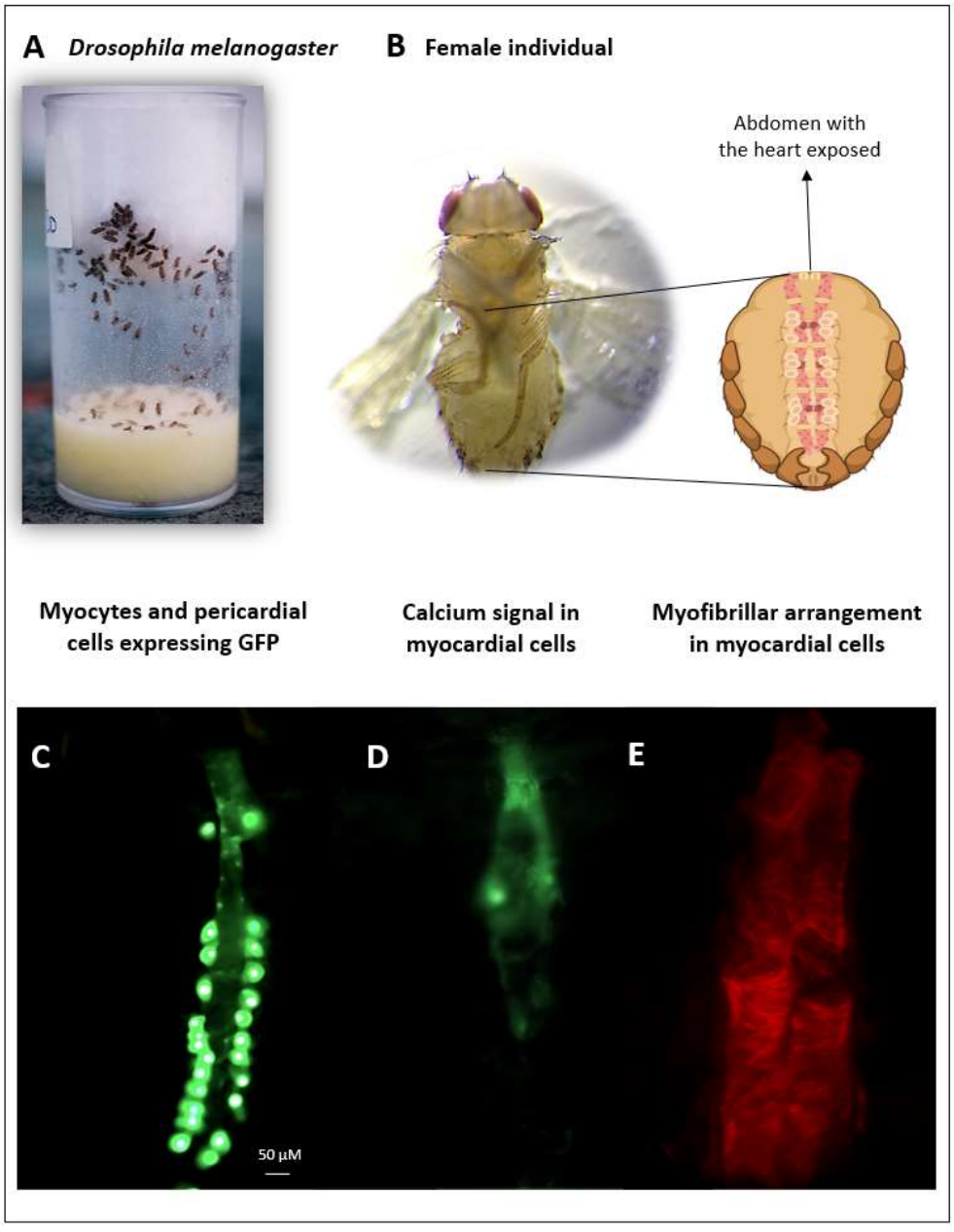

Figure 1. A. Adults individuals of wild type *Drosophila melanogaster* growing into a vial. **B.** Aspect of a female individual and scheme of an opened abdomen to visualize the heart. C-D. Two transgenic approaches to recognize structures and intracellular mediators: **C.** Cardiomyocytes and pericardial cells expressing a green fluorescent protein (GFP) under the driver *Hand C*. **D.** Cardiac-specific expression of Ca^{2+} sensing fluorescent protein used to assess intracellular Ca^{2+} transients in the cardiomyocytes. **E.** Myofibrillar arrangement of the cardiac fibers identified with phalloidin (magnification 40X).

Drosophila and diseases

Almost all human organ systems have a counterpart in the fruit fly [8]. Below is shown how the major organ systems of *Drosophila* have contributed to understanding human physiological processes and pathologies. Figure 2 represents the correspondence between the most important system in humans and flies.

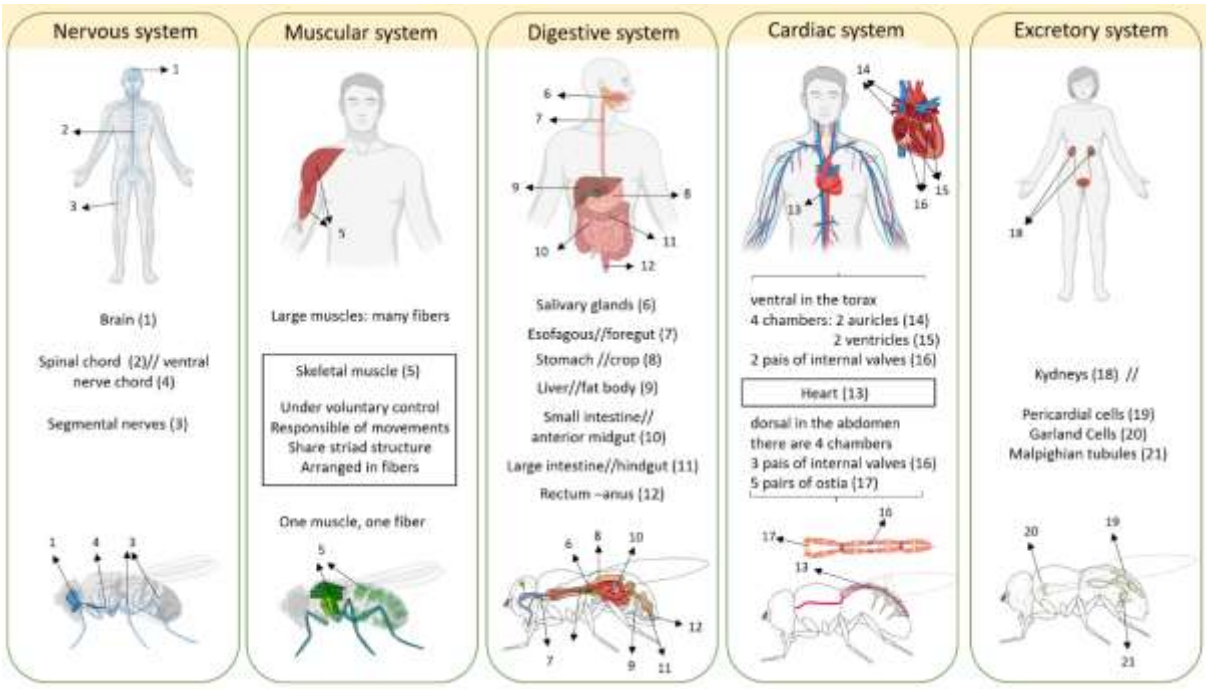

Figure 2. Comparison of the human and *Drosophila melanogaster* organ system of interest in biomedical research. Each organ is numbered and indicated in the correspondent scheme.

Nervous system

The central nervous system of *Drosophila* consists of a bilateral and symmetrical brain, composed of neurons and glial cells [9]. From there, neuronal extensions extend to the rest of the body. Many human neurological disorders can be modeled in the fruit fly. One of them is Parkinson's disease (PD) which is characterized by progressive deterioration of motor functions. Inherited forms of PD are caused by mutations in genes encoding key proteins in the development of the pathophysiology of the disease. Most of the genes implicated in familial forms of PD have at least one homolog in the fly, such as LRRK2, parkin, PINK1, and DJ-1 and the pathways regulated by these genes are also conserved in this organism [10]. Several key neuropathological and clinical features of PD are reproduced in this model because flies can perform complex motor behaviors such as walking, climbing, and flying.

Alzheimer's disease is a progressive neurological disorder that results in the irreversible loss of neurons in the cortex and hippocampus. The formation of amyloid plaques and neurofibrillary aggregates are characteristic events. Transgenic flies that model this pathology overexpress the gene coding for presenilin, a component of the alpha-secretase complex which induces an intracellular calcium deficit and is related to one of the early events of Alzheimer's pathology. Other models are based on the expression of the human gene tau, which allows the analysis of myofibrillar aggregates detected in this pathology. In addition, there are models of co-expression of the beta-amyloid precursor protein and human tau [11].

Another pathology that has been reproduced in fruit flies is Friedreich's Ataxia, an autosomal recessive disease. The mutation conducts to loss of function of the gene encoding the frataxin protein [12]. Patients present a neurodegenerative disorder that causes motor problems and in a subgroup of individuals, hypertrophic cardiomyopathy [13]. Moreover, it is possible to model epilepsy, a neurological disorder characterized by sudden recurrent episodes of sensory and motor disturbances caused by abnormal electrical activity in the brain. Some types of epilepsy are caused by genetic factors such as mutations in genes that code for ion channels. There are models of epilepsy in *Drosophila* with mutations in *eag* and *sh* genes. Their products are components of potassium channels and mutant flies show neuronal hyperexcitability and seizures [14].

The scheme of neurodegenerative disorders that can be modeled in *Drosophila* also includes amyotrophic lateral sclerosis, spinocerebellar ataxia, and Huntington's disease [9]. On the other hand, as in humans, sleep disorders have a major impact on the physiological functions of *Drosophila* and might even lead to death. Since many of these disorders have a genetic component, it is possible to study the molecular mechanisms associated with these alterations by modifying the homologous of the human gene in the fruit fly.

Cardiac system

The adult *Drosophila* heart is a longitudinal tube extending along the abdomen in the dorsal region. It consists of four chambers arranged in series and connected by valves. The entry of hemolymph into the chambers occurs through the ostia. Hemolymph is the intracellular fluid that provides nutrients and hormones to the internal organs of the fly. Unlike mammals, the respiratory system is composed of tracheas and provides gaseous exchange independently of hemolymph circulation. This characteristic allows flies to live for days with a severely damaged heart and allows drastic interventions to be made in the circulatory system with less impact on the rest of the body's tissues and organs [15]. Genes encoding for contractile proteins such as channels, pumps, and other proteins present in cardiomyocytes are conserved between *Drosophila* and mammals [16].

Drosophila can present heart failure and, as in humans, it can be distinguished between dilated and hypertrophic cardiomyopathies. Cardiomyopathies secondary to other types of disorders can be detected in fruit flies. For example, mutants for the presenilin gene, associated with early-onset Alzheimer's disease, present dilated cardiomyopathy. Changes in the expression levels of this gene increase age-associated arrhythmias, mitochondrial and myofibrillar degeneration [17]. Regarding the channelopathies, KCNQ potassium channels have been studied during aging and it has been demonstrated that they play a protective role. Mutations of the KCNQ1 channel, lead to prolonged QT syndrome causing cardiac arrhythmias [18]. In models of diabetes, flies subjected to a diet enriched with sugar were observed to develop cardiomyopathies associated with insulin resistance and type 2 diabetes. Increased arrhythmias and impaired cardiac function modulated by insulin and MAPK pathways were observed [19].

In addition, flies have been sent to the space to examine the effects of microgravity on cardiac structure and function to understand the changes that astronauts might undergo in space missions. Exposure to microgravity resulted in structural and functional cardiac remodeling, reduced output along with decreased expression of genes encoding for sarcomere and extracellular matrix elements in flies [20].

Digestive system

The *Drosophila* and mammalian intestine are of endothelial origin. Both of them include a monolayer of cuboidal epithelial cells called enterocytes, as well as stem cells. Mammalian and *Drosophila* intestinal cells (ISCs) share intracellular mechanisms that control intestinal regeneration. Due to the physiological similarities between the *Drosophila melanogaster* and

vertebrate gut, the midgut epithelium of the fruit fly has been used to study the contribution of signaling pathways (*i.e.*, EGFR, Notch, Hedgehog, and Wg/Wnt) to the renewal of stem cells (Stem cells ISCs) [21]. Also, *Drosophila* constitutes a model organism for high-throughput studies on gut microbiota-host interactions. The intestinal mucosa must distinguish between commensal, mutualistic, and pathogenic bacteria. The imbalance between components of the microbiota can disrupt intestinal homeostasis and lead to disorders [22].

Excretory system

In humans, podocytes, specialized cells in the glomeruli of the kidneys, are responsible for filtration. Analogous cells in the fruit fly are nephrocytes, present in the thorax, named Garland cells, and in the abdomen, named pericardial cells. It has been possible to model conditions such as diabetic nephropathies and monogenic forms of nephrotic syndromes in *Drosophila* [23].

Pathologies with multiorgan impact

Aging

Aging in all organisms can be described as the deterioration of various functions over time until death occurrence. In *Drosophila*, the ability to feed oneself, as well as mobility, resistance to stress, and fertility, are reduced over time. Sleep disturbances are common. Neurological functions such as learning and memory are impaired. Old flies frequently exhibit heart failure [24]. Aging reduces heart rate and alters intracellular calcium handling. Thus, aging affects multiple organ systems simultaneously.

Obesity

Obesity increases the risk of diabetes, metabolic syndrome, cardiovascular disease, and cancer. Therefore, uncovering the complications associated with obesity is challenging. *Drosophila* has been used to model obesity induced by a diet rich in sugars and fatty acids. In *Drosophila*, the organ that stores carbohydrates and lipids are the fat body, analogous to human adipose tissue. Obese individuals accumulate triglycerides in the fat body. The fat body also performs liver-like functions. Flies with high sugar intake, like humans, exhibit hyperglycemia, insulin resistance, and cardiomyopathies. Obesity in fruit flies can also be genetically induced to analyze the consequences of obesity without altering nutrient-sensitive signaling mechanisms [25].

Diabetes

Diabetes is a chronic metabolic disease caused by deficiency or loss of insulin. *Drosophila* produces seven insulin-like peptides secreted by insulin-secreting cells in the brain. These peptides participate in signaling pathways similar to those in mammals. It is possible to model type I and type II diabetes in *Drosophila.* As in mammals, high-sugar diet leads to insulin resistance. This is accompanied by decreased weight and increased glucose in the hemolymph and fat body in larvae as in adults [27].

Cancer

Cancer is a disease based on deregulation in the activity of oncogenes and/or loss of function of tumor suppressor genes, often induced by environmental factors that increase the risk of developing the disease. Most of the signaling pathways linked to cancer development are present in *Drosophila*. Cell polarity mediators and pathways such as Salvador-Warts-Hippo (SWH), RAS/RAF/ERK, PI3K/TOR, JNK, and cMyc, deregulated in cancer, can be also altered in the fruit fly [27].

A summary of human diseases modelized in *Drosophila* is shown in figure 3.

Drosophila and drugs

Drug addiction is a disorder characterized by excessive use of one drug, to the point of compulsive drug seeking and use. This can lead to dependence on the substance, which includes physical symptoms such as tolerance and withdrawal. Although addiction is considered a human phenomenon, animal models provide insight into the molecular mechanisms underlying addictions. Flies exhibit complex behaviors such as associative learning, sensor-motor integration, and social behaviors [28]. This has allowed to used them in the study of the effects induced by various substances of abuse.

Alcohol

Ethanol is a known substance to fruit flies because it is found in nature as a product of sugar fermentation. In the laboratory, studies focus on the locomotor response to acute ethanol exposure, tolerance to the compound, and preference behaviors that model aspects of addiction. For example, male flies rejected by previously mated females showed a preference for consuming ethanol-supplemented food. Interestingly, although virgin males showed a preference for ethanol-supplemented food, this was not greater than that manifested by rejected males. The researchers demonstrated that sexual deprivation would create a deficit of a specific peptide (neuropeptide F, NPF) that would increase reward-seeking behavior, such as ethanol consumption [29].

Caffeine

Caffeine has been used in experiments in which sleep deprivation has been induced in *Drosophila*. Utilizing this strategy, it was possible to compare insomniac individuals treated or not with compounds such as γ-aminobutyric acid (GABA) and 5-hydroxytryptophan (5-HTP), both proposed as candidates in the search for drugs that can solve sleep problems. On the other hand, in our laboratory, we observed that the application of caffeine in the hemolymph of *Drosophila* has direct effects on the heart modifying the heart rate and the force of contraction [30].

Cocaine

Studies on the action of cocaine focused on behavior and neurophysiology in *Drosophila* showed similar results that human responses to this substance. Flies that consumed cocaine had altered dopamine levels causing increased adult mortality and defects in the formation of female reproductive cells (gametes). Other defects observed in the formation of gametes in these flies were attributed to the dysregulation of another neurotransmitter, serotonin [31].

Amphetamines

Amphetamine and methamphetamine are used clinically to treat attention deficit hyperactivity disorder and narcolepsy, among other conditions. Long-term use of these compounds creates the risk of addiction. Side effects of methamphetamine in humans, like increased oxidative stress, heart failure, neurotoxicity have been reported, among others. In *Drosophila,* methamphetamine causes toxic effects like in humans. It was observed that exposure of flies to this substance, increased locomotor activity and induced anorexia. It has also been identified that these substances affect the set of several genes (genome) and proteins (transcriptome) [31].

Cannabis

Mammals and other vertebrates respond to phytocannabinoids. These compounds are present in the flowers of the *Cannabis sativa*, known as marijuana. Phytocannabinoids are similar in structure and/or function to components of the vertebrate endocannabinoid system. This system regulates many functions such as pain response, nutritional status, and overall balance of the body. Fruit flies possess endocannabinoids in their hemolymph although the most studied cannabinoid receptors in mammals, CB1 and CB2, are not present in insects [32]. However, other receptors mediate responses to cannabinoids in mammals, such as the transient receptor potential channels (TRPs) and peroxisome proliferator-activated receptors (PPARs). Numerous actions of cannabinoids cannot be explained by binding to CB1 and CB2 receptors. Thus, the interest on alternative pathways mediated by other receptors, is increasing. Studies from our laboratory have shown that the behavior and cardiac function of healthy flies exposed to phytocannabinoids, were affected. Chronic treatment with a strain rich in the cannabinoid tetrahydrocannabinol (THC) initially increased arrhythmias. However, longer exposure to phytocannabinoids induced increased contractility [33].

Nicotine

Nicotine has been shown to influence the development and survival of *Drosophila melanogaster*. The gene encoding for the nicotinic cholinergic receptor is present in *Drosophila melanogaster* and it has been shown that nicotine increases heart rate in larvae, which have the particularity that their heart is not innervated. The cardiac muscle of *Drosophila melanogaster* also presents receptors for glutamatergic neurons and beta-adrenergic receptors that connect with the nervous system, on which the mechanisms of action of nicotine are known in more detail. Studies of our group have shown that flies chronically exposed to tobacco presented an incremented heart rate and alterations in the dynamics of the calcium transient in the heart. Mutant organisms for the alpha 1 and 7 subunits of nicotinic receptors allowed us to elucidate the relative contribution to the observed effects of tobacco and nicotine [34].

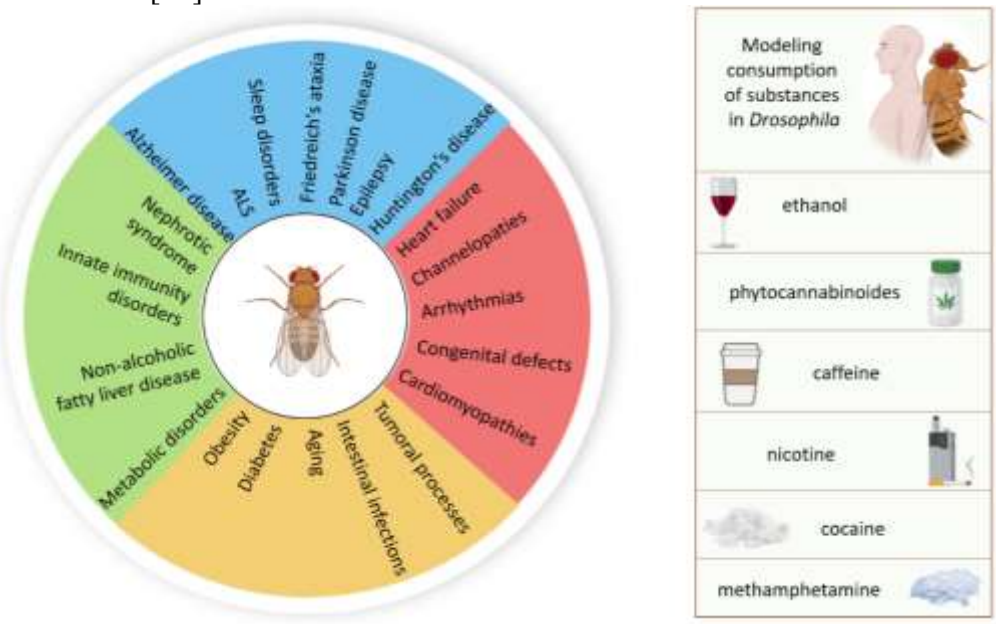

Figure 3. Left: Different diseases can be modelized in the fruit fly. Right: list of substances of human consumption studied in *Drosophila*.

Pharmagenomics

Finally, *Drosophila melanogaster* is a useful organism for high-throughput pharmacological studies, accelerating the discovery of new compounds for therapeutic purposes [35]. Pharmacogenomics analyzes the response of the genome to drugs. This discipline allows to determine which drugs and doses are adequate for patients, according to their genetic polymorphisms. High-throughput studies in flies, whose genome is completely sequenced, conduct to the identification of genes responsible for different responses to substances. Thus, it might be possible to find new drugs for subsequent trials.

Although many human pathologies have been mentioned that can be investigated in *Drosophila*, this model has limitations like other animal models. Oher pathologies of different etiology than genetic origin cannot be easily modeled or the results cannot be safely extrapolated to humans. Disease modeling reproduces some but not all symptoms. Complex polygenic diseases are more difficult to address. However, the versatility of the model after more than 100 years of research history, turns it into a possibility to be explored through studies in new areas of biomedical disciplines.

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She is a researcher of the National Council of Scientific and Technical Research (CONICET) at the Cardiovascular Research Center, National University of La Plata, and Associate Professor of Pharmacogenetics at the University of Northwestern of Buenos Aires.

Ferrero is head of the laboratory of *Drosophila melanogaster* at the Cardiovascular Research Center. In her lab, *Drosophila melanogaster* is used as a model for studying human diseases focusing on cardiac pathophysiology. Among her projects are the study of the effects of cannabis administration in two lines of Parkinson diseases and epilepsy *in Drosophila melanogaster,* both involving cardiomyopathies. Dr Ferrero's lab is also involved in the study of circulating microRNAs in patients with Chagas diseases, to identify a specific pool of microRNAs with diagnostic and prognostic value for Chagasic cardiomyopathy.