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Antidiabetic Research: A Review of *Drosophila melanogaster* Models, Molecular Mechanisms, and Experimental Protocols

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Abstract
Drosophila melanogaster has emerged as a valuable model organism for investigating metabolic disorders, particularly in the realm of diabetes research. It effectively replicates the intricate nature of human diabetes, making it an ideal subject for creating diabetes models. Its acceptance as an experimental model stems from several factors, including the simplicity of genetic manipulation, cost-effectiveness, and time efficiency. The conservation of insulin signalling and metabolic pathways between *Drosophila melanogaster* and mammals further underscores its relevance in elucidating human diabetes mechanisms. Studies have shown that *Drosophila* are used as an experimental model to show the antidiabetic activity of numerous plants such as *Cyperus rotundus L. Kombucha*, *Potentilla discolor Bunge, Spondias mombin (Linn),* Soy isoflavone and *Atriplex halimus.* Successful research outcomes with *Drosophila melanogaster* depend largely on maintaining optimal culture conditions and employing techniques that minimize stress and injury to the flies. This review examines the significance of *Drosophila melanogaster* in antidiabetic research, encompassing the underlying molecular mechanisms, experimental protocols, applications in drug screening and the challenges associated with utilizing this model organism.

Keywords: *Drosophila melanogaster,* Diabetes modelling, Antidiabetic plants, Culturing of fruit fly.

Introduction

Diabetes, a metabolic condition characterized by high blood sugar levels, is becoming more widespread worldwide (Khan et al., 2020). The primary source of glucose in the body is dietary sugar, which is broken down into monosaccharides before being absorbed and transported to cells and tissues for metabolic processes (Bai et al., 2018). However, excessive sugar intake can disrupt the body's glucose balance, leading to obesity and other metabolic issues such as fatty liver and hypertension, ultimately resulting in type 2 diabetes mellitus (Khan & Sievenpiper 2016).

Managing post-meal blood sugar spikes is essential for diabetes prevention (Zaki et al., 2021). Blood glucose levels are influenced by various factors, including enzymes that break down carbohydrates, the incretin system, and glucose transporters. Additionally, markers of inflammation are recognized as indicators of diabetes outcomes (Lüersen et al., 2023).

Drosophila melanogaster, commonly known as the fruit fly, has become an important model organism in biomedical studies. It has gained prominence in genetic, neuroscience, physiological, and disease modelling research, particularly for studying metabolic disorders like diabetes. With its uncomplicated genetic structure, quick reproductive cycle, and conserved biological pathways, *Drosophila* has been extensively utilized to explore the molecular mechanisms of diabetes and screen potential therapeutic agents (Alfa & Kim 2016).

Similar to human physiology, *Drosophila* possesses insulin-producing cells, insulin-like molecules, and an insulin-responsive mechanism (Partridge et al., 2011). Characteristics resembling insulin resistance, such as metabolic

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disorders and impaired insulin signalling, can be replicated in both larval and adult stages of *Drosophila* (Morris et al., 2012).

Using *Drosophila* as diabetes models offer an ideal system for identifying bioactive compounds for diabetes management, enhancing the understanding of the underlying molecular mechanisms, and broadening the approaches against the disease (Liu et al., 2020). Furthermore, insulin deficiency in *Drosophila* results in stunted growth and reduced body length in both larvae and adults. This easily observable trait facilitates high-throughput screening of small molecule compounds that promote growth in insulin secretion-deficient mutant *Drosophila*. The application of this model in drug discovery, screening, and validation stages shows great promise (Miao et al., 2022).

Drosophila melanogaster **as a Diabetes Model**

The fruit fly presents an opportunity to investigate diabetes through various research methods (Figure: 1), potentially advancing the understanding of the disease and yielding practical applications.

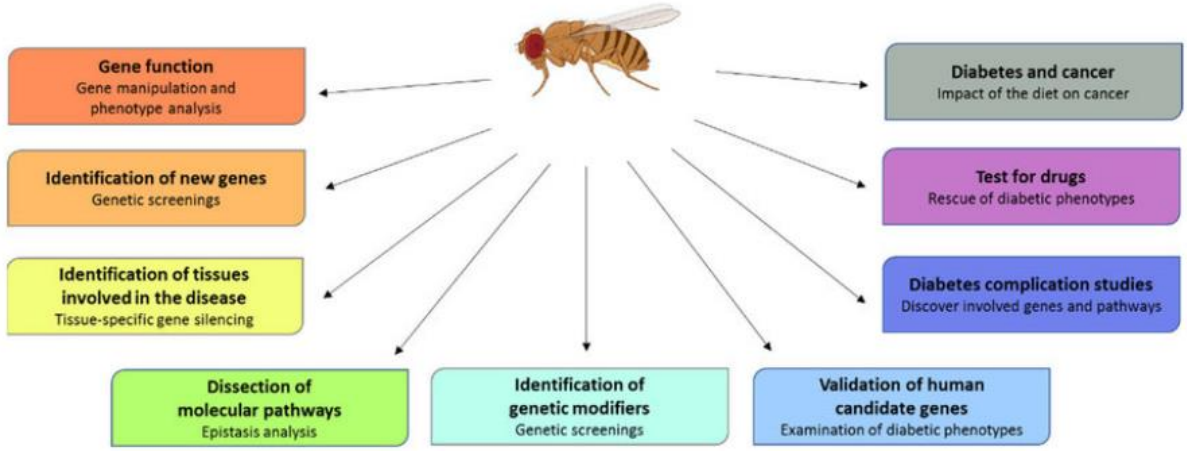

Figure 1: Advantages of using *Drosophila* for diabetic studies
Source: Liguori et al., 2021

Diabetes, a metabolic condition characterized by insulin resistance and/or deficiency, encompasses both Type 1 and Type 2 variants with distinct origins. Although *Drosophila* lacks certain organs like the pancreas, it shares numerous crucial metabolic pathways with humans, particularly those related to insulin signalling, glucose metabolism, and energy balance (Grönke et al., 2010). The genome of fruit flies contains homologs to various mammalian genes involved in glucose regulation, including insulin receptors, insulin-like peptides, and enzymes crucial for glucose metabolism (Zhang et al., 2009).

Glucose homeostasis is maintained in a remarkably conserved manner in *Drosophila*. Flies possess insulin and glucagon counterparts which perform the same functions as the mammalian hormones. Eight genes encode *Drosophila* insulin-like peptides (DILPs), designated DILP1 to DILP8. Among these proteins, DILP2, DILP3 and DILP5 are involved in the regulation of hemolymph glucose levels and fat storage, and in the control of development, body size and longevity (Nässel et al., 2013)

In insects, energy metabolism is primarily regulated through insulin/IGF signaling (IIS), TOR signaling, and adipokinetic hormone (AKH) signaling (Miao et al., 2022). These pathways are preserved across animal species, including insects and humans, enabling the creation of models to investigate the genetic and molecular mechanisms underlying diabetes and to screen potential antidiabetic compounds for targeted therapies (Herranz & Cohen 2017). Researchers have developed multiple fly strains exhibiting diabetes-like characteristics, such as elevated blood sugar, insulin resistance, impaired insulin release, glucose intolerance and abnormalities in carbohydrate metabolism, closely mirroring human conditions. The capacity to perform precise genetic alterations in *Drosophila* allows scientists to generate models that replicate specific aspects of diabetes. This has significantly enhanced the comprehension of the

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molecular mechanisms underlying the disease (Zhang et al., 2009; Kumar et al., 2016; Honegger et al., 2008; Graham & Pick 2017).

Beyond its genetic advantages, *Drosophila* has a lifespan of approximately 60-70 days and can produce numerous offspring rapidly, making it a cost-effective model for high-throughput drug screening. This makes it ideal for evaluating a wide array of potential therapeutic agents within a relatively brief period (Ogienko et al., 2022)

Modelling of Diabetes in *Drosophila*

Drosophila's utility in diabetes research stems from its capacity to simulate both type 1 and type 2 diabetes through genetic manipulation of insulin signalling and glucose metabolism pathways. These models have shed light on diabetes pathophysiology and potential treatments (Liguori et al., 2021)

Type 1 diabetes, characterized by insufficient insulin due to the destruction of insulin-producing cells, can be replicated in *Drosophila* by eliminating insulin-producing cells or blocking insulin release. For example, mutations affecting the function of insulin-producing cells (IPC) in the *Drosophila* brain led to decreased insulin secretion and elevated blood sugar levels, mirroring Type 1 diabetes symptoms (Honegger et al., 2008). Such models enhance the understanding of insulin deficiency's role in diabetes development and allow for testing interventions that might boost insulin production or substitute its function.

Type 2 diabetes, primarily marked by insulin resistance and impaired glucose uptake, can be simulated in *Drosophila* by disrupting insulin receptor (InR) function or altering insulin-like peptide (DILP) expression. Introducing dominant-negative InR forms in fat body cells or neurons results in insulin resistance and high blood sugar levels, closely resembling Type 2 diabetes in humans (Kumar et al., 2016). Additionally, modifying DILP expression in *Drosophila* has been shown to induce insulin resistance and obesity, offering a valuable model for studying Type 2 diabetes progression and the effects of insulin-sensitizing agents (Sarkar & Whitley, 2014).

A method to induce Type 2 diabetes symptoms in *Drosophila* through high-sugar diets has been established (Palanker et al., 2011). Studies have shown that high-sugar diets trigger clear signs of insulin resistance in *Drosophila,* which is the primary pathology of Type 2 diabetes in humans (Teleman, 2010; Murillo-Maldonado & Riesgo-Escovar, 2017). The documented effects of high-sugar diets on *Drosophila* include elevated blood sugar levels, insulin resistance, increased fat accumulation, and reduced lifespan (Na et al., 2013). Scientists have explored the impact of botanical extracts on preventing metabolic disturbances caused by high sucrose consumption in *Drosophila.* Furthermore, fruit flies possess the glucosidase enzyme, which is vital for sugar adaptation (Dechakhamphu et al., 2023)

Recent advancements have addressed the limitation of *Drosophila* not exhibiting long-term diabetic complications seen in humans, such as nephropathy, neuropathy, and retinopathy. *Drosophila* model to investigate glucose-induced retinal neurodegeneration was developed. The research revealed that hyperglycemia caused by a high-sugar diet (HSD) resulted in eye defects, disrupted apoptosis/autophagy regulation, oxidative stress, and visual impairments (Catalani et al., 2021). This model provides an opportunity to explore the molecular mechanisms and pathophysiology of neuroretina changes characteristic of early-stage diabetic patients.

Diabetic nephropathy (DN), a significant secondary complication, leads to dysfunction in glomerular and renal tubular systems. A recent study demonstrated that HSD-fed *Drosophila* could serve as a model for identifying genes and mechanisms involved in renal tubular dysfunction in DN (Rani et al., 2020). The researchers discovered that fly Malpighian tubules, which are functionally equivalent to vertebrate kidneys, replicate many aspects of diabetes-induced renal tubular dysfunction. These include AGEs-receptor for AGEs (RAGE) signalling, apoptosis, and expression of genes associated with DN pathways. This finding established a suitable model for investigating the underlying mechanisms of this pathology.

Culturing and Maintaining *Drosophila* for Diabetes Studies

Maintaining robust *Drosophila* populations is essential for reliable diabetes research outcomes. *Drosophila melanogaster* is typically reared in glass or plastic containers with a specialized nutrient medium. This medium, often yeast-based agar, contains ingredients such as sugar, cornmeal, and yeast, along with preservatives like propionic acid

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to inhibit Mold growth. The containers require breathable covers, frequently made of cotton or foam, to facilitate air circulation while preventing fly escape. Optimal laboratory conditions for *Drosophila* include regulated temperatures (generally 22°C to 25°C) and a 12-hour light/dark cycle (Ashburner et al., 2005). Proper fly care is vital for extended diabetes studies, as stressed or overcrowded populations may yield inconsistent results due to resource competition or environmental pressures. Exposure to extreme temperatures can alter insulin sensitivity or cause metabolic abnormalities in flies, potentially skewing diabetes study results (Sullivan et al., 2000). Maintaining appropriate environmental conditions is crucial, particularly when investigating phenomena like stress-induced insulin resistance.

Aspirators are frequently employed to gently move flies between containers or experimental setups. To isolate specific genotypes, researchers can sort male and female flies using aspirators or advanced techniques based on genetic markers or physical traits such as eye colour or body size (Greenspan, 2004). Accurate fly sorting by sex and genotype is essential for maintaining proper experimental conditions, especially when examining sex-specific variations in diabetes susceptibility or treatment efficacy.

To minimize stress and injury during experiments, flies are often sedated using carbon dioxide (CO_2) or cold exposure. CO_2 anaesthesia is common in genetic and behavioural studies but must be applied cautiously to avoid prolonged exposure, which may affect fly health (Bauer & Weber, 2008). Alternatively, cooling flies on ice induces temporary immobility and is preferred in some studies as a less stressful method. Cold anaesthesia is generally considered gentler and less likely to harm the flies compared to CO_2 exposure (McEwen & Gould, 2016).

Methods of Screening Antidiabetic Drugs in *Drosophila*

Various methods are employed in screening antidiabetic drugs in *Drosophila melanogaster* model, these include;

In Vivo Methods

- **High-Calorie Diet-Induced Diabetes:** Flies are fed a high-sucrose diet to induce insulin resistance and type 2 diabetes.
- **Genetic Models:** Flies with genetic modifications that mimic type 2 diabetes, such as insulin receptor mutants, are used to study drug effects.
- **Glucose Feeding Assays:** Flies are fed a glucose-rich diet, and drug effects on glucose levels are measured (Karthikeyan, et al., 2016)

In Vitro Methods

- **Isolated Tissue Assays:** Isolated fly tissues, such as fat bodies or muscles, are used to study glucose uptake and insulin signalling.
- **Cell-Based Assays:** Fly cells are used to study insulin signaling pathways and glucose metabolism (Zheng, et al., 2018)

Phenotypic Assays

- **Locomotor Activity:** Flies' locomotor activity is measured to assess drug effects on energy metabolism.
- **Survival Assays:** Flies' survival rates are measured to assess drug effects on longevity.
- **Glycogen and Trehalose Measurement:** Glycogen and trehalose levels are measured to assess glucose storage and metabolism (Omale, et al., 2021).

Utilizing *Drosophila* for Screening Antidiabetic Agents

A key use of *Drosophila* in diabetes studies is evaluating potential antidiabetic medications. The fruit fly model has demonstrated its effectiveness as a platform for assessing new compound efficacy. Research has uncovered both natural substances and FDA-sanctioned medications that enhance insulin responsiveness or decrease high blood sugar levels in *Drosophila* diabetes models (Ashrafi et al., 2014). In recent years, multiple investigations have utilized *Drosophila* to search for substances that control glucose metabolism, boost insulin sensitivity, or restore insulin secretion.

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Table 1: Recent investigations of antidiabetic plants using *Drosophila* as an experimental model.

Extract	Parameters	Effect	References
Cyperus rotundus L. Kombucha	DPPH, ABTS, SOD, CAT, H_2O_2, alpha glucosidase and Protein	Enhance the activity of antioxidant enzymes, reduce dietary sugar absorption	(Dechakhamphu et al., 2023)
Atriplex halimus L, Moringa oleifera Lam, Tagetes patula L, Morus nigra L, Atriplex halimus L, Morus nigra L.	Glucose and trehalose, larva weight,	Recover the symptoms of type 2 diabetes.	Hanaa et al., 2021
Spondias mombin (Linn)	Locomotor, glucose, total thiol, nitric oxide, Lipid peroxidation, ILP2, InR and IMPL2	Exhibited antioxidant property, restored glucose homeostasis and Up-regulation of ILP2, InR and IMPL2	Omoboyowa et al., 2023
Parinari curatellifolia	Glucose, total protein, total diol, AChe, CAT, NO, GST	restored normal glucose levels, remarkable antioxidant effects, improved growth and development	Omale et al., 2021
Soy isoflavone	protein and triglyceride	reduction of the triglyceride content	Lüersen et al., 2023
Geum urbanum L. (avens root)	Weight, Triglyceride and Protein	reduced body weight and triglyceride content	Günther et al., 2021
Atriplex halimus	Glucose, trehalose, larval weight, DILP2 and DILP3, AKH	Decrease in total glucose, trehalose, DILP2, DILP3, and AKH	Montaser et al., 2024
Potentilla discolor Bunge	growth rate, glucose, genes of the JAK/STAT signalling pathway (Impl2 and insulin receptor inhibitor Socs36E)	Improvement of insulin resistance by inhibiting the JAK/STAT signalling pathway.	Ying et al., 2023
	glucose, trehalose, and triglyceride	improving Akt activity and decreasing CASP3 expression	Li et al., 2024
Bayberry leaves proanthocyanidins	Weight, glucose, triglyceride, alpha amylase and alpha glucosidase, DILP2 and DILP3, InR	ameliorated the symptoms of HSD-induced dysglycemia, downregulated DILP2, DILP3 and InR	Wang et al., 2022

glutathione-S transferase (GST), Acetylcholinesterase (AChe), Nitric oxide (NO), insulin-like peptides (DILP2 and DILP3) and adipokinetic hormone (AKH), insulin receptor (InR), nsulin like-peptide 2 and 3 (DILP2 and DILP3)

Limitations and Challenges in Using *Drosophila* for Antidiabetic Studies

Although *Drosophila* has been instrumental in diabetes research, its utility in modelling human diabetes has certain constraints. A significant drawback is the absence of a pancreas in *Drosophila*, an organ crucial for insulin secretion in humans. Instead of a dedicated organ, flies store glycogen in their fat body and produce insulin-like peptides in

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specialized cells within their brain and fat body (Geminard et al., 2009). This difference complicates direct comparisons between *Drosophila* and mammalian diabetes models (Zhang et al., 2009).

Moreover, the fly model lacks the intricate hormonal and metabolic interactions found in humans, potentially restricting its ability to replicate the full range of diabetic complications and treatment responses. While *Drosophila* can offer valuable insights into the molecular pathways underlying insulin resistance and glucose metabolism, it may not fully capture the long-term effects of diabetes or accurately model aspects like insulin secretion and the complex hormonal feedback mechanisms regulating glucose homeostasis (Slonim et al., 2009, Grönke et al., 2010).
Despite these shortcomings, *Drosophila* remains a powerful tool for examining the genetic and molecular mechanism of diabetes and evaluating potential therapies. The simplicity of the fly's system enables researchers to investigate specific diabetes-related pathways and provides a cost-effective, high-throughput model for drug discovery (Lopez-Ortiz et al., 2023).

Conclusion

Drosophila melanogaster has proven to be an invaluable tool in antidiabetic research. The genetic tractability, short lifespan, lower cost in experimental protocol and its ability to model key aspects of insulin signalling and glucose metabolism make it an excellent model for the study of potential therapeutic agents in diabetes. Despite there are limitations in terms of physiological differences between flies and humans, *Drosophila* is still providing valuable contributions to the molecular understanding of diabetes. Furthermore, the integration of *Drosophila* models with other systems, such as mammalian models, rodents and human cell cultures, might allow a broader view of diabetes pathogenesis and lead to the discovery of novel therapeutic strategies.

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