

Fruit Flies: From Model Organism to Medical Marvel in Pharmaceutical Research

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ABSTRACT

Fruit fly, or *Drosophila melanogaster*, is becoming a cornerstone model organism for biomedical research as a result of its genetic tractability, affordability, and high conservation of genetic pathways with humans. *Drosophila* has developed from a classical genetics model to a robust system for research into human diseases and drug discovery. The small body size, brief life cycle, and high reproductive rates of the fruit fly render it a suitable organism for big-scale, high-throughput researches. Around 75% of disease-causing genes in humans have functional homologues in *Drosophila*, enabling scientists to explore a broad range of diseases such as neurodegenerative disorders, cancers, epilepsy, metabolic syndromes, cardiovascular diseases, and infectious diseases. It's completely sequenced genome, along with sophisticated genetic manipulative tools like CRISPR, RNAi, and transgenic technologies, enables specific gene manipulation. Behavioral and physiological tests from memory assays to seizure susceptibility allow functional *in vivo* studies. Drug discovery applications are broad, with routes of administration from feeding to inhalation and injection. Fly models have been employed in assessing drug efficacy, screening new compounds, and delineating pharmacogenetic heterogeneity. Technological innovations now allow seamless integration with human genotype-phenotype databases, making *Drosophila* more useful in translational research. In addition, the model has helped in the discovery of novel targets for treatments and evaluating toxicity and environment impact. *Drosophila melanogaster* remains a vital tool in deciphering disease mechanisms and the design of new therapeutic intervention. This review provides the overview and applications of fruit flies in various diseases.

Keywords: *Drosophila melanogaster*, Epilepsy, Fruit flies, Neurodegenerative diseases, RNAi.

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INTRODUCTION

Genetics and bio-medicine research have long relied largely on the fruit fly, *Drosophila melanogaster* (Atoki *et al.*, 2025). From a simple genetic model to a powerful tool for the investigation of human disease, *Drosophila* has evolved further (Verheyen 2022). Its application is not limited to classical genetics but extends to developmental biology, neuroscience, and, more recently, disease modeling and drug discovery. Genes conserved in humans are surprisingly common in the *Drosophila* genome, which consists of four chromosomes and 180 megabases (Loesche *et al.*, 2021). *Drosophila* is a valuable model for investigating a multitude of diseases, from metabolic syndrome and viral infections to neurodegenerative and cancer, since it contains functional

homologs of more than 75% of human disease-causing genes (Obafemi *et al.*, 2025).

The organism's entire genome has been sequenced, and a myriad of genetic tools have been developed to specifically manipulate and study gene expression. In addition, *Drosophila* is an ideal model for understanding complex biological mechanisms due to its comparatively simple body plan, which allows extensive phenotypic analyses. In early biomedical research, *Drosophila* is one of the ethical alternatives to vertebrate models due to the increased focus on the 3R principles- Replacement, Reduction, and Refinement (Kratsios *et al.*, 2024). Reduction refers to the strategy of examining the experimental design to ensure that the number of experimental animals utilized in a study has been reduced to the minimum requirement to achieve sufficient results. Replacement refers to measures that replace or avoid the use of experimental animals altogether (Vashishat *et al.*, 2024). Refinement refers to process improvements that minimize the adverse effects of the proposed studies on the involved animals, e.g., decreasing pain, suffering, and distress in a manner that encourages overall animal welfare (Madden *et al.*, 2020). Through their roles as *in vivo* models for the study of disease biology and



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evaluation of pharmacologic interventions, model organisms remain a critical component of pre-clinical drug discovery. A shift towards more simple and ethically acceptable models has been prompted by growing concern with animal rights and welfare.

SPECIES OVERVIEW

Generally referred to as the fruit fly or vinegar fly, *Drosophila melanogaster* is a dipteran fly within the family of *Drosophilidae*. *Drosophila* neurogenetic models have served to elucidate the mechanisms behind brain development and synaptic transmission (Duhart *et al.*, 2022). Further, it is an excellent model with which to explore signaling pathways conserved in humans and commonly associated with disease, such as Notch, Hedgehog, and Wnt. *Drosophila* is an excellent choice for high-throughput research because of its small size and minimal laboratory needs (Kumar *et al.*, 2021). Its tractability in genetics also allows for the development of transgenic lines and RNAi knockdowns to analyze gene function *in vivo*. Most significantly, genes like Toll-like receptors (TL), homeobox, *dunce* (*dnc*), and *period* (*per*) were first discovered in *drosophila* and subsequently known to have homologs in humans. Fruit fly is an ideal organism to study gene function, interactions, and disease causation owing to its relevance (Yusuf *et al.*, 2022).

ADVANTAGES

Genetic Simplicity and Manipulability

Drosophila differs from other model organisms in that both loss-of-function and gain-of-function tests are simple to conduct. As accurate genetic alterations are provided by CRISPR and transgenic technologies, RNA interference (RNAi) enables precise silencing of genes (Li *et al.*, 2020).

Speed and Cost-Effective Breeding

Flies are readily cultured in the laboratory, requiring little space. Compared to vertebrate models like rats and mice, they are also less expensive to maintain and hence allow large-scale and high-throughput research.

Advanced Behavioral and Physiological Assays

Drosophila is an organism that has simple behavioral and physiological responses. For evaluating learning and memory, motor function, response to pain, and even aggression, assays have been established (Sarkar *et al.*, 2023).

Versatility in Disease Modeling

A large variety of human diseases have *drosophila* models. These include metabolic conditions (obesity, diabetes), cardiovascular and infectious diseases, neurological diseases (such as Alzheimer's, Parkinson's, and Huntington's), and various cancers.

PATHOPHYSIOLOGICAL RELEVANCE

Due to the strong path route conservation of genes in flies compared to human beings, *Drosophila melanogaster* is an appropriate model to model human diseases. *Drosophila* is applied in cancer research to describe the functions of tumor suppressor and oncogene genes (Yamamura *et al.*, 2021). Neurodegenerative diseases such as Huntington's, Parkinson's, and Alzheimer's have been illuminated using *Drosophila* models in neuroscience. Transgenic flies with human disease genes reproduce the key clinical features, allowing for functional study and drug screening. Using seizure-sensitive mutants that respond to drug therapies similar to those in humans, the model has also significantly informed us about epilepsy. The Toll and Imd routes in flies report on inflammatory and infectious diseases by simulating innate immune responses in mammals (Fischer *et al.*, 2023).

APPLICATIONS

Neurodegenerative diseases

Drosophila has played a major role in helping us understand the molecular origins of neurodegeneration. Human disease genes have been expressed in flies to imitate a variety of illnesses, including Huntington's, Parkinson's, and Alzheimer's (Kashyap *et al.*, 2023). These models often exhibit traits like motor impairment, protein aggregation, and neuron death. Toxic protein aggregation is frequently observed in these models. For example, flies with neurodegeneration caused by the polyglutamine-expanded huntingtin protein can be saved by drugs that block Histone Deacetylase (HDAC). This increases the likelihood of therapeutic potential and permits *in vivo* drug screening. Figure 1 highlights the importance of *drosophila* in neurodegenerative diseases.

Drug discovery

The utility of *Drosophila melanogaster* in drug development continues to expand and its ability to adapt for high-throughput screening, genetic manipulation, and *in vivo* phenotypic study. Potential therapeutic chemicals for a variety of illnesses, such as cancer, epilepsy, diabetes, and neurodegenerative disorders, are screened for using *drosophila* models (Lopez-Ortiz *et al.*, 2023). The effectiveness of anti-epileptic pharmaceuticals, for instance, has been evaluated using seizure-prone fly mutants such as *eas2F* and *parabss1*, which exhibit dose-dependent reactions to different anti-seizure treatments. Flies have also been used to model pharmacogenetic variability and medication resistance, which can help identify new therapeutic targets (Fischer *et al.*, 2024). *Drosophila* is a useful model for early-stage drug discovery because of its low cost, ease of maintenance, and less ethical considerations. The translational potential of this system can be seen by the success of a MEN2 thyroid cancer medication that was developed using a *drosophila* model.

Cancer research

The majority of human oncogenes and tumor suppressor genes, including Ras, p53, and PTEN, have homo-logs in fruit flies (Lappalainen *et al.*, 2021). By modifying these genes in genetically modified flies, scientists may create tumors and track the resulting phenotypes. For instance, the molecular changes observed in human malignancies appear in *Drosophila* by over activation of cell proliferation pathways and abnormalities in epithelial integrity (Munnik *et al.*, 2022). *Drosophila* speeds up the process of finding potential medications and treatment targets for cancer research. shares human tumor suppressor genes and conserved oncogenes (Figure 2). *Drosophila* tumorigenesis is a genetic and cellular model of human cancer development (Nainu *et al.*, 2023).

Neurological disorders[Epilepsy]

Drosophila melanogaster provides a genetically tractable model for researching seizure causes and discovering Anti-Seizure Drugs (ASMs) in the field of epilepsy research. Fly models that resemble human epileptic phenotypes, such as bang-sensitive mutants (e.g., eas2F, parabss1), exhibit seizure-like behaviors in response to mechanical stimuli (Yamamoto *et al.*, 2024). These include initial convulsions, transient paralysis, and recovery seizures. It's interesting to note that various medications behave differently in particular mutants, suggesting that drug reactions vary by genotype. This implies that pharmacogenetic variability in humans can be simulated using *Drosophila*.

Diabetes and metabolic diseases

A useful model for researching diabetes and metabolic syndrome is *Drosophila melanogaster*. Central to this is the *Drosophila* Insulin-Like Peptide (DILP) system, which mirrors mammalian insulin in function and control. Elevated glucose and lipid levels in the hemolymph, the fly equivalent of blood, result

from disruption of insulin-producing cells in the fly brain. This mimics the hyperglycemia and dyslipidemia observed in diabetes individuals (Miguel Sanz *et al.*, 2023).

Cardiovascular diseases

These models aid in the investigation of potential medications for obesity, cardiovascular disease, and metabolic syndrome. Both pathological and functional cardiac conditions in *Drosophila* and mammals have been associated with autophagic abnormalities in cardiovascular architecture and cellular dysfunction. Additionally, it has been used to model cardiomyopathies such as restrictive, hyper-trophic, and dilated cardiomyopathy, which can result in heart failure, as well as cardiac aging (Kervadec *et al.*, 2023).

Infectious diseases

The Toll and Imd pathways in *Drosophila* are linked to innate immune responses and apoptosis, much like mammalian immune signaling. Bacteria with LYS-type peptidoglycan in their cell walls (mostly Gram-positive bacteria) trigger the Toll pathway, whereas DAP-type peptidoglycan (mostly Gram-negative bacteria) triggers the IMD route. Following the translocation of NF- κ B dimers to the nucleus, these pathways result in the over expression of AMPs that are specifically targeted to eradicate the infection (Souidi *et al.*, 2021). The ability of flies to assess antibacterial responses is demonstrated by antibiotic research employing medications such as amoxicillin and tetracycline. Antibiotic tolerance mechanisms involving the persistence of *E. coli* have even been evaluated using the fruit fly model.

Genetic and functional studies

It simplifies the process of identifying and evaluating the roles of important genes and genes connected to disorders. Despite being thought of as a model organism best suited to investigating basic genetic and biological issues, flies are increasingly being employed

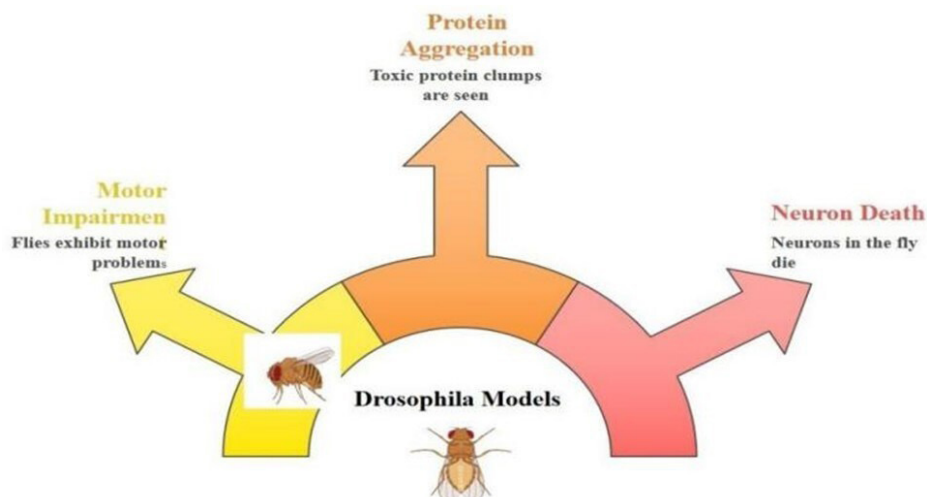


Figure 1: Application of *Drosophila* in Neurodegenerative diseases.

as a powerful tool to explore the mechanisms underlying human genetic disorders. *Drosophila*'s advanced genetic tools enable geographically and temporally controlled gain-of-function and loss-of-function investigations of the target genes. Fruit flies are extremely relevant for researching the genetic basis of human diseases, such as neurodegenerative disorders (like Parkinson's, Alzheimer's, and fragile X syndrome), cancers, diabetes, cardiovascular diseases, and infectious diseases, since they share roughly 75% of the genes that cause disease with humans (Chen *et al.*, 2023).

Pharmacogenetics

Fruit flies (*Drosophila melanogaster*) have been used extensively in pharmacogenetics, the study of how genetic diversity affects medication response. Fruit flies are a potent model for investigating gene-drug interactions and pre-clinical drug discovery. Gene-drug interactions that are significant for human health are often revealed by *Drosophila* models used to screen for anticancer, anti-epileptic and analgesic drugs (Jain *et al.*, 2021). Similar to human neuropharmacology, fruit flies are employed to

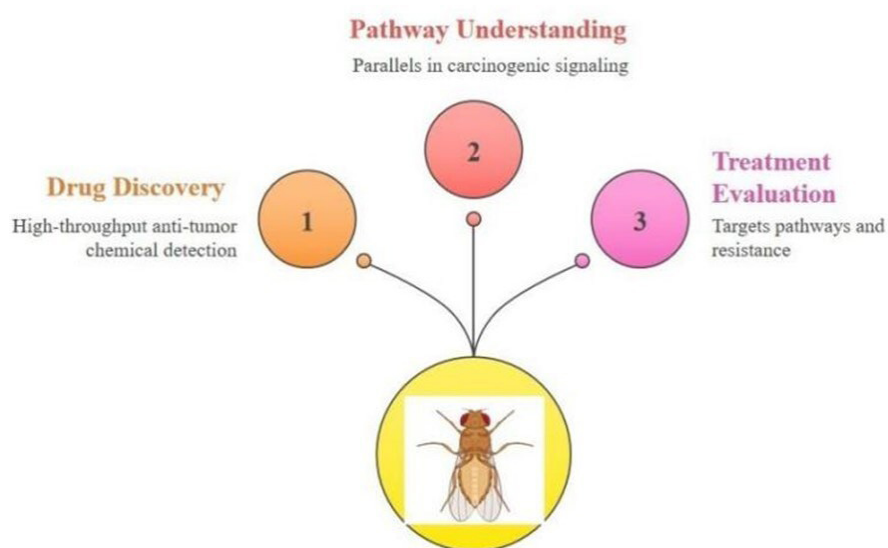


Figure 2: Role of *Drosophila* in Cancer Research.

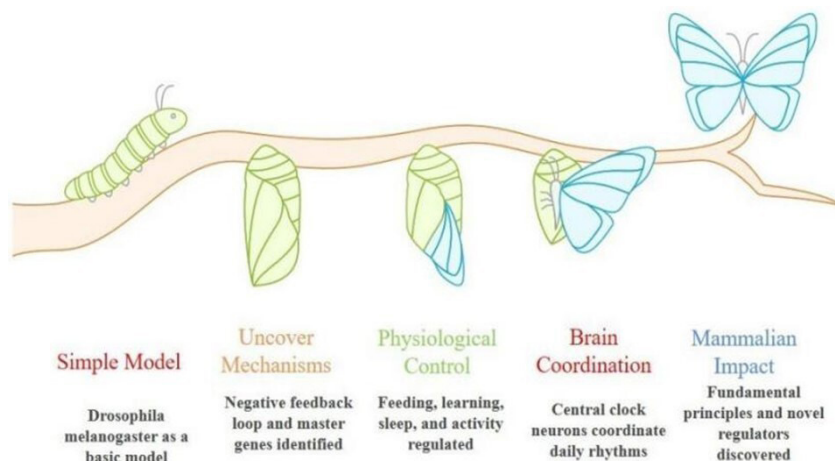


Figure 3: Circadian Clock Model of *Drosophila*.

investigate the genetic underpinnings of drug-induced behavioral alterations.

Drosophila as a Model for the Circadian Clock

The genetic tractability and functional simplicity of *Drosophila melanogaster* have rendered it a basic model organism for unraveling the genetic, molecular, and neurological processes underlying the circadian clock. The work in drosophila uncovered the mechanism of the negative feedback loop that generates 24-hr rhythmic cycles, which is highly conserved in mammals, and identified master clock genes such as period and timeless. These have been key to understanding the evolution, mechanisms, and control of circadian rhythm (Figure 3). Many physiological and behavioral processes, such as feeding, learning, sleep, and locomotor activity, are controlled by the circadian clock in drosophila, which also coordinates cycles within the brain and other organs. Mammalian circadian biology has been impacted by drosophila findings directly through, and it is now a powerful tool for discovering fundamental principles and novel circadian

regulators with far-reaching implications for human health (Asiri *et al.*, 2024).

Pleiotropic Actions of Statins on Fruit Fly Metabolism and Development

Fruit flies (*Drosophila melanogaster*) possess genetic mechanisms controlling cholesterol that are highly conserved with humans and therefore provide a good model to study the actions of statins on cholesterol metabolism. Statins such as simvastatin have been found to exactly replicate the pleiotropic (cholesterol-independent) benefits exhibited in humans by increasing lifespan and enhancing cardiac function in old flies. This effect is most probably resulting from alterations in protein prenylation and not cholesterol levels. Since drosophila retains the statin target HMG-CoA reductase and muscle physiology, the animal can also be employed to examine statin side effects, including those related to muscle. Different research works done on drosophila is represented in Table 1.

Table 1: Research works done on fruit flies as animal model.

Type	Drug	Diseases
Panneuronal OE of Tau, (Elav-Gal4)	paclitaxel	Alzheimer's disease and Parkinson's.
Surf1	Bezafibrate	Alzheimer's disease
<i>Drosophila simulans</i> strain	Cisplatin, Dacarbazine, and Daunorubicin	Alzheimer's disease and cancer.
Transient receptor potential (TRP) and PIEZO-type mechanosensitive channel components (PIEZO)	Capsazepine, Yohimbine, Carvacrol, Rosiglitazone	Parkinson's and Alzheimer's diseases.
<i>C. elegans</i>	Levamisole	Parkinson's and Alzheimer's diseases.
Ras (Rasv12)	Sotorasib (Lumakras) and adagrasib	Cancer research, cell biology
ΦC31 recombination-mediated cassette exchange (RMCE)	Blasticidin S HygromycinB G418 sulfate (geneticin)	Parkinson's and Alzheimer's diseases, Amyotrophic Lateral Sclerosis and prion diseases.
UAS-GAL4, LexA-lexAop, QF-QUAS,	Sulphonyl ureas	Diabetes.
Drosophilalarval heart	Atropine	Larval heart function [Rhythmic control.], cardiac rate.
Wntfamily homolog wingless (wg) and the BMP family homolog decapentaplegic (dpp)	Oxazole, thiazole, and thiazolidinedione	Limb formation, embryonic development, cardiomyocytes.
slowpoke, shaker, and ether-a-go-go,	4-aminopyridine (4-AP)	Pacemaker regulation, ion channel.
Eiger, Insulin, Wnt inhibitor of dorsal (WntD)	Oxazole, Thiazole, Thiazolidinedione	Innate immunity.
Chico gene	4-phenylbutyrate (PBA)	Enterococcus faecalis and P. aeruginosa infections.

TECHNOLOGICAL ADVANCES AND FUTURE POTENTIAL

The application of *Drosophila* in human disease modeling has been increasing with advances in genomics and gene editing technologies (Yoon 2023). Fly biology research has been combined with novel resources, such as human genotype-phenotype databases, that facilitate the annotation of gene functions and the identification of novel therapeutic targets. Some recent examples are the identification of new pain receptors (e.g., the painless member of the TRP family), studies on inflammation and enteropathy with NSAID's, and the application of gut microbiota models to investigate conditions such as depression, obesity, and Crohn's disease (Swierczynski *et al.*, 2023).

CONCLUSION

Drosophila continues to bridge the gap in information from basic research to clinical utility, from causative disease mechanism discovery to drug therapy assessment. It is a phenomenal tool for investigating the complexities of human disease and health. The perfect model organism is *Drosophila melanogaster* since it is genetically tractable, ethically responsible, experimentally tractable, and translationally valuable. Its numerous scientific breakthroughs have made our knowledge of biology and disease what it is today, and its future use will be thought to speed up the identification of new treatments. *Drosophila* as a species will undoubtedly be leading the way in biomedical innovation as research all over the world is attracted to less ethical and more sustainable methods.

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ABBREVIATIONS

AMPs: Antimicrobial peptides; **ASMs:** Anti-seizure drugs; **CRISPR:** Clustered regularly interspaced short palindromic repeats; **DAP:** Diaminopimelic acid; **DILP:** *Drosophila* insulin-like peptide; **HDAC:** Histone deacetylase; **HMG-CoA:** 3-hydroxy-3-methylglutaryl-coenzyme A; **IMD:** Immune deficiency; **LYS:** Lysine; **NSAIDs:** Non-steroidal anti-inflammatory drugs; **PBA:** 4-phenylbutyrate; **RMCE:** Recombination-mediated cassette exchange; **RNAi:** RNA interference; **TRP:** Transient receptor potential; **UAS-GAL4:** Upstream activating sequence - GAL4.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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