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Review Article

**DROSOPHILA MELANOGASTER – VERSATILE MODEL FOR  
THE STUDY OF HUMAN DISEASES**Rutuja S. Abhonkar <sup>1\*</sup>, Sagar R. Bagul <sup>2</sup><sup>1</sup>Assistant Professor, Department of Pharmacology, Swami Vivekanand Sanstha's Institute of Pharmacy, Mungase, Malegaon, Nashik, India.<sup>2</sup>Aurigene Discovery Technologies, Department of In-vivo Pharmacokinetics & Bioanalysis, Bengaluru, Karnataka.

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**Abstract:**

*The fruit fly Drosophila Melanogaster is a popular model system in genetics labs that combines genetics and developmental biology. Drosophila genetics is tractable, but its embryonic development was too complex and intractable to study until molecular biology tools made gene manipulation and RNA extraction from these species possible. D. Melanogaster is quickly becoming one of the most powerful tools for studying the function of human disease genes, such as those involved in developmental and neurological disorders, cancer, cardiovascular disease, metabolic and storage diseases and genes involved in the visual, auditory and immune systems. Flies have various experimental benefits, including a fast life cycle and ability to create huge numbers of individuals, making them suitable for sophisticated genetic screening and in future aiding in the investigation of complicated disorders. This review considers the broad concept through which D. Melanogaster can be utilised to compare human disease, as well as its advantages and life cycle.*

**Keywords:** *Drosophila Melanogaster, life cycle, Human disease model, Good model organism, Endocrinology of drosophila*

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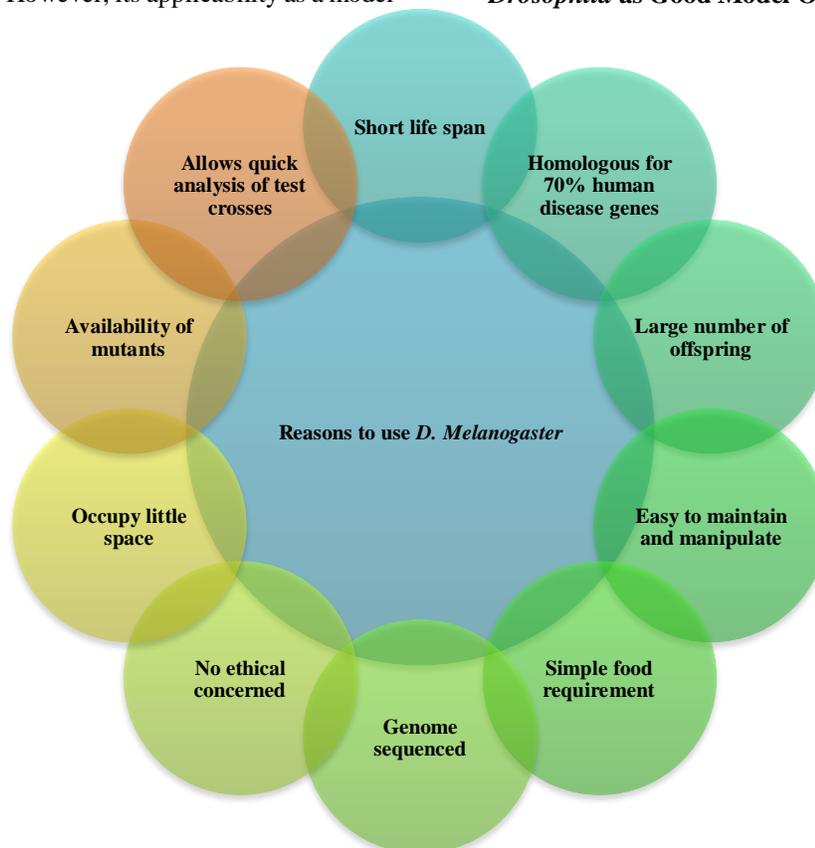


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**INTRODUCTION:**

The *Drosophila* genus (family) which incorporates *Drosophila melanogaster* is a member of order diptera, as a holometabolous insect, *Drosophila* undergoes a complete metamorphosis, including a progress from larval to pupal structure, the total life cycle consist of four phases [1]. The fruit fly has made considerable progress since Charles W. Woodworth, an American entomologist, first proposed to utilize *Drosophila melanogaster* as a genetic model organism in 1900 [2]. Humans and *Drosophila* have many conserved genes. However, its applicability as a model

system extends beyond basic gene comparisons. Entails the study of a wide range of cellular and developmental processes. Along with the similarity in appearance, basic cellular structure and function, humans and *Drosophila* having same intercellular signalling pathways [3]. Around 75% of human disease-causing genes are believed to have a functional homolog in flies [4]. *Drosophila melanogaster* played a vital part in characterising how genes function in time and space to control advancement.

***Drosophila* as Good Model Organism:**

**Fig. 1: Advantages of drosophila as a model organism [5].**

**Life Cycle:**

*Drosophila* is a simple organism to keep for, reproduce, and manipulate. Flies can be housed in vials and given a cornmeal, glucose, agar, and fungicide-based diet medium [6]. The entire life cycle of *Drosophila* is relatively short, taking about 10–12 days at ambient temperature. The stages of *Drosophila* development are as follows: Embryo, larva, pupa, and adult are the four stages of development (Fig. 2) [7]

**1. Egg:**

*Drosophila* egg is about 0.5mm elongated, white oval and slightly flattened on lateral view. An inner extremely thin vital line envelope encompasses the

ovum alongside an external extracellular coat called chorion. Two small respiratory filaments which extend from dorsal surface, at the anterior end which is recognized by the structure on the external coating surrounding the egg called micropyle, after fertilization and fusion of the sperm and egg, zygote nucleus divisions at the initial stage of development of the embryo [8, 9]. Many sperms may penetrate an egg, but only one sperm function in fertilization is generally performed. The female has been storing the spermatozoa since the time of the mating. Immediately following the entrance of the sperm, the reduction (meiotic) divisions of sperm are

finished, and the egg nucleus (female pronucleus) is created. The mother may lay the eggs soon after the sperm has penetrated them, or they may be maintained in the uterus until the early phases of embryonic development [10].

## 2. Larval Stage:

Larva undergoes two molts after hatching from the egg. Larval period comprises three stages; the third stage may achieve a length about 4.5mm. The larva is strongly dynamic and unquenchable feeders that the culture medium in which they are creeping becomes heavily channelled and furrowed [9]. Larva has 3 head segments, 3 thoracic segments and 8 abdominal segments, soft and versatile body wall and contains outer non-cellular cuticle and inner cellular epidermis. Over the entire body great numbers of sense organs are regularly spread. Circulatory organ of the larva is the dorsal blood vessel. The larval muscles, segmentally arranged, transparent but that are visible when the

larva contains a variety of primitive cell complexes called imaginal discs, which are primordial for later imaginal structures [9, 11].

Larva is grown by the initial mechanism; molting. Whole cuticle of the insect, including many specialized cuticular structures, as well as the mouth armature and the spiracles is shed and must be revamped again, and therefore many reconstruction processes occur at every molt. Internal organ growth is slowly proceeds and appears to be independent of the molting process, which mostly affects the body wall. Malpighian tubes, muscles, fat body, and intestine grow by increasing the size of their cells; the number of cells in the organ remains constant. Organ discs, on the other hand, increase primarily by cell multiplication, while individual cells remain around the same size. In general, strictly larval organs grow by increasing cell size, whereas presumptive imaginal organs grow by increasing cell multiplication [12].

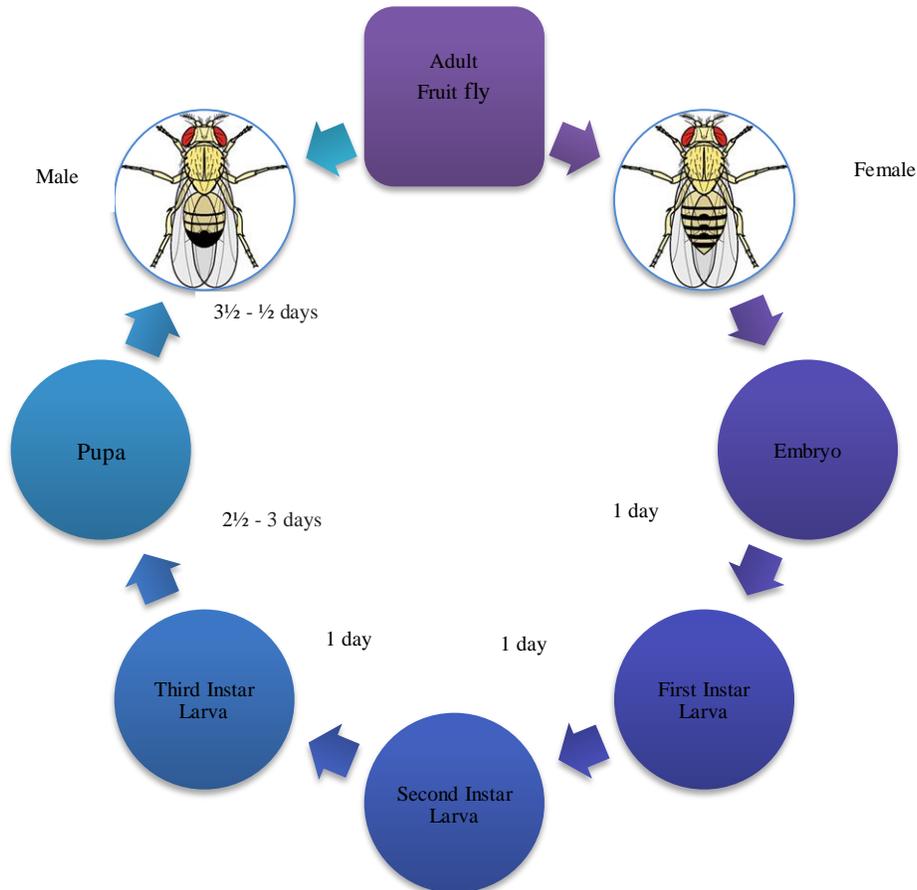


Fig. 2: The whole life cycle of the fruit fly.

*Drosophila* is relatively rapid and takes only approximately 10–12 days at 25° C. The *Drosophila* development is divided into various stages: embryo,

### 3. Pupa

Metamorphosis is a series of developmental processes by which an insect transforms from a larval to an adult creature. During the pupa stage, the metamorphosis process undergoes the most significant changes. Larva leaves the food shortly before pupation and creeps up the edges of the culture bottles, looking for a suitable place to pupate, before ultimately coming to rest. The larva has grown exceedingly large, has averted its anterior spiracles, and has stopped moving. Soon after, the larva shortens and looks to be a little wider, forming its pupa shape. The contraction of the larval cuticle, which forms the puparium's case, is induced by muscular action. The outer pupal case, or puparium, is similar to the cuticle of the last larval instar. The larval segmentation is destroyed when the puparium has finished forming, but the cuticle remains white. This stage lasts only a few minutes, making it an accurate time marker for determining the pupa's age. The hardening and darkening of the cuticle begin immediately after it reaches the white prepupal stage and progress swiftly. The puparium is fully coloured after about three and a half hours [11, 13]. The animal within the puparium has detached its epidermis from the puparium four hours after it was formed, and has become a headless creature with no external wings or legs, known as the "prepupa." The prepupa is surrounded by a very fine prepupal cuticle that has been secreted [14]. Pupation occurs roughly 12 hours after the puparium is formed. The prepupa contracts its muscles. The halteres, wings, and legs are also averted. The head, thorax, and abdomen of a typical pupa are shaped in this way. The pupa is now enclosed by three membranes: an exterior membrane, the puparium; an intermediate membrane, the prepupal cuticle; and an inner membrane, the freshly secreted pupal cuticle [15]. Now, metamorphosis entails the destruction of some larval tissues and organs (histolysis) as well as the organisation of adult tissues and organs. The imaginal discs are structures derived from primitive cell complexes. It should be noted, however, that some larval organs are toxic. Without any major changes, they were changed into their imaginal state, their structure changed. For the various organs involved, the time and extent of these transformation processes varies substantially. The salivary glands, fat bodies, gut, and apparently muscles are the only larval organs that undergo complete histolysis during metamorphosis. All of these organs are created from scratch, either from imaginal disc cells already existing in the larva or from

larva (first instar, second instar and third instar, pupa and adult)

cells that emerge during pupal restructuring. Although the structural composition of malpighian tubules does not vary much throughout metamorphosis, it does change slightly. The brain, which is not entirely histolyzed, appears to be in the same state. Imaginal discs, which were previously present in the larval stage and undergo histogenesis during pupal development, differentiate the extremities, eyes, mouthparts, antennae, and genital apparatus. Imaginal disc cells also make up the body walls of the imaginal head, thorax, and abdomen. All imaginal discs in this region work together to construct the body wall of the head and thorax, each contributing their portion. The hypoderm of the abdomen is made up of segmentally arranged imaginal cells that first appear in immature pupae [16].

### 4. Adult Stage

Adult flies emerge from the pupa case once transformation is complete. Their wings are not fully developed, and they are delicate and pale in colour. In a few hours, these flies darken and take on the look of an adult fly [17]. Flies are pale in colour when they first emerge, but they darken after a few hours. This criterion can be used to separate newly emerging flies from older ones in the same culture bottle. They survive for a month or more before dying. After emerging from the pupa, a female does not mate for roughly 10 to 12 hours. She saves a large amount of sperm in receptacles after mating and fertilize her eggs as she lays them. As a result, it is vital to employ females who have never mated previously in order to assure a regulated mating. Virgin females are the name given to these flies [11].

### Features to determine the sex of adult fly

For determination of sex first observe size of fly. This is the first and most fundamental step in determining *Drosophila's* gender. Female flies are much larger than male flies. Because this strategy is not always effective, you must be ready to look further into the differences. Then look at the abdomen. The abdomen of a fly is made up of several segments. The last two segments of the abdomen of a male fly are substantially darker than those of a female. Females have a single darker band on the bottom with a lighter band on top, whilst males have broad black bands. The female's abdomen is pointed, but the male's is rounded at the bottom. Examine the sex combs under a microscope. Because sex combs are always present, this is the greatest technique to identify between

male and female flies. A microscope will very certainly be required to see sex combs. A simple 10x microscope will work. Male flies have sex combs on their forelegs, which appear as thick black lines just

before the joint. If you look closely, you'll notice that they're lifted off the leg and pointed at the end (Tab. 1).

**Tab. 1. Features to determine the sex of adult fly.**

Features	Female	Male
Size of adult [10]	Females are often larger than males.	Males are smaller
Shape of abdomen [10]	In females, the tip of the abdomen is extended.	Abdomen is more rounded in male.
Markings on the abdomen [11]	On the entire back portion of the female, there are alternating dark and light bands. With low power magnifiers, the female's abdomen has seven parts that are easily apparent.	On the back portion, the last few segments are fused in male.  Abdomen of male has five segments.
Appearance of sex comb [18]	Such bristles are lacking in the female.	Males have sex combs, which are a fringe of approximately ten thick black bristles on the distal surface of the foreleg's basal (uppermost) tarsal segment.
External genitalia on abdomen [14]	The female's ovipositor is located at the tip of her abdomen and is pointed.	The male's claspers are darkly pigmented, circularly organised, and positioned immediately ventral to the tip.

#### ***D. Melanogaster's* endocrinology**

*D. melanogaster's* endocrine glands are derived from epithelial tissues and act similarly to vertebrate glands at the molecular and cellular levels. For example *D. melanogaster*, has circulating hormones. Plasma membrane receptors PMRs and nuclear receptors (NRs) are two types of receptors found on the plasma membrane, are controlled by the same chemical and biological processes. Mechanisms discovered in vertebrates' hormonal systems PMRs and NRs are encoded in *D. melanogaster's* DNA that correspond to several human receptor subtypes, those involved in neurotransmission [19]. Ecdysone and Juvenile Hormone are the two principal hormonal systems in *D. melanogaster*. Ecdysone is a steroid hormone produced in the prothoracic glands that is analogous to cholesterol-derived steroid hormones like estradiol. Juvenile Hormone is a sesquiterpenoid produced in the corpora of the *D. melanogaster's* brain, and it resembles retinoic acid in several ways [20]. Ecdysone controls and precedes the moult in the *D. melanogaster*. Juvenile hormone production stops at the end of the third instar larva, allowing ecdysone to reach its peak, allowing pupation, cell death, and the formation of new cellular structure to begin. In the

adult stage, juvenile hormone affects spermatogenesis, longevity, locomotion, nutrition, secondary sexual differentiation, and courting. It also works together with ecdysone to help with fertility [21]. As previously stated, fruit fly development regulation shares some chemical and biological similarities with vertebrate development regulation; nevertheless, the influence of traditional developmental toxicants in mammals has been little investigated in *D. melanogaster* [22].

#### ***Drosophila melanogaster* used as promising model organism in various studies:**

##### **1. *D. melanogaster* to Assess Oxidative stress and antioxidant Biomarkers:**

We are in the era of free radicals and oxidative stress in biomedical sciences. Indeed, experimental evidence has linked oxidative stress to the pathogenesis of a number of diseases [23]. Several studies using *D. melanogaster* to assess oxidative stress and antioxidant markers have been published in the literature. Depending on the quantities of the indicators of relevance to the toxicologist, each assay may require a different technique. For example, the technique of homogenising the treated and control

flies in appropriate buffers, centrifugation at an appropriate speed and temperature, and determining biochemical and molecular markers of relevance to the toxicologist using the separated supernatants can be used [24].

**2. *D. melanogaster* in neurodegenerative diseases:** Human neurodegenerative disorders disproportionately afflict the elderly and are linked to life-threatening conditions. Pathogenic oligomers caused by misfolded proteins are linked to important neurodegenerative illnesses including Alzheimer's and Parkinson's, resulting in the slow loss of neurons in the nervous system and brain [25].

#### **Huntington's disease:**

Another polyglutamine disorder studied in *Drosophila melanogaster* is Huntington's disease. It is an autosomal dominant neurodegenerative condition characterised by choreic movements that develop over time, as well as cognitive impairment and behavioural disorders. It is now thought to be caused by aberrant polyglutamine expansion at the huntingtin protein's N-terminus. When the number of repeats is increased beyond 36, the neurotoxic huntingtin protein that causes Huntington's disease is produced [26]. Homologues of the huntingtin protein have been discovered in other vertebrates, including mice, puffer fish, and zebrafish, although functional domains of the protein could not be differentiated due to similar amino acid sequences. Studies on the more distantly related *Drosophila* have led to the discovery of conserved protein domains that are thought to be important in the Huntingtin protein's function [27].

#### **Parkinson's Disease:**

Parkinson's disease is a late-onset movement condition with three primary symptoms: resting tremor, stiffness, and bradykinesia. Progressive degeneration of dopamine neurons in the substantia nigra pars compacta, as well as the development of cytoplasmic neuronal aggregates known as Lewy bodies, are the neuropathological hallmarks of this disease. The majority of cases are sporadic, however missense variants in the  $\alpha$ -synuclein gene (A53T and A30P) have been linked to the disease and have been discovered in autosomal dominant families. Parkinson's disease is a neurological disorder that affects people [28]. Despite the fact that these mutations are an uncommon cause of familial Parkinson's disease,  $\alpha$ -synuclein is a key component of Lewy bodies in the brains of both familial and

spontaneous Parkinson's disease patients [29], suggesting that the protein may have a key role in the development of both types of the disease. By producing wild-type and mutant versions of human-synuclein in flies, a *Drosophila* model of Parkinson's disease has been created [30]. Human  $\alpha$ -synuclein expression in flies mimics major neuropathological characteristics of Parkinson's disease.

#### **Alzheimer's disease**

Alzheimer's disease is the most common cause of dementia in the world, and it's characterized by external amyloid plaques and intracellular neurofibrillary tangles, as well as neuronal loss. TAU, a microtubule-associated protein, is aggregated and hyper phosphorylated in neurofibrillary tangles. The finding of TAU gene mutations in FTDP-17 families provides convincing evidence that TAU malfunction is directly linked to neurodegeneration. A *Drosophila* model that may be used is associated with Alzheimer's disease and frontotemporal dementia. Dementia is a relatively new term by expressing mutant and wild-type versions of fruit flies with human TAU [31]. The model replicates numerous aspects of the actual illness, including age-related, progressive neurodegeneration, relative specificity of neuronal loss, premature death, and build-up of inappropriately phosphorylated forms of TAU in neurons. Ataxia causes considerably more severe neurodegeneration. Extra pyramidal flies that express mutant TAU are more common in patients than flies that express the wild-type protein. Surprisingly, neurodegeneration can take place without the development of neurofibrillary tangles. TAU's neurotoxic effects may be supplied through protein changes such as phosphorylation, rather than by tangle formation, at least in *Drosophila*.

#### **3. Fly Base Resource in the study of *D. Melanogaster***

Toxicologists interested in using *D. melanogaster* as a model can access a number of online resources. For toxicologists interested in this model, the FlyBase database (<http://flybase.org>) is a highly useful and comprehensive internet-based resource. The Fly Base contains vital information on accessible mutant alleles, knockdown lines, human disease homologs, and whole-genome sequences in *D. melanogaster*. Fly Base also offers connections to a number of stock centers at various universities, where particular requests for the fruit fly may be fulfilled [25]. Fig. 3 is showing the Fly Base home page (<http://flybase.org>).

Fig. 3: Flybase Home Page [39].

#### 4. *D. melanogaster* in Cancer study

In cancer research, *D. melanogaster* is increasingly being employed as a model system. Cancer research used to be restricted to mammalian-based techniques like tissue culture and whole-animal investigations [32]. The use of *D. melanogaster* in cancer research has led to the discovery of several things, including the signalling pathway that coordinates cell proliferation and death, cell competition and apoptosis-induced compensatory proliferation, and the mechanism of oncogenes and tumour suppressor cooperation [33].

#### 5. *D. melanogaster* in cardiovascular diseases

Certain elements of cardiovascular illnesses induced by environmental factors have been successfully modelled using the fruit fly. This is due to the fact that the heart growth of the fly is dependent on specific genes that have been passed down through the generations of mammals [34]. In flies, several cardiac dysfunctions have been discovered, some of which are age-related, such as cardiomyopathies, structural abnormalities, and arrhythmias [35]. *D. melanogaster* has made it simple to assess the effects of pharmacological drugs on heart function using a variety of approaches that are outside the scope of this article.

#### 6. *D. melanogaster* in Inflammation and Infectious Diseases:

Because *D. melanogaster* is continuously exposed to infections in the environment, it has evolved a complex immune response that can help researchers

better understand human inflammatory diseases. *D. melanogaster* has been used to simulate some types of inflammatory diseases, such as asthma, in a similar way to humans [25].

#### 7. *D. melanogaster* in Metabolic Disorders and Diabetes

*D. melanogaster* can be utilized as a model to investigate some elements of human metabolism, such as glucose homeostasis and endocrinology, according to the research. In the brain, it has insulin-like peptide-secreting cells [36], and extra glucagon analogue secretory cells, making it physiologically comparable to the endocrine system of vertebrates [37]. In reality, flies have been employed to research type 2 diabetes metabolic processes [38], however because to the lack of a liver and pancreas, its application in this field is restricted.

#### CONCLUSION:

*D. melanogaster* continues to be a valuable model organism for studying basic elements of cell biology and development. *D. melanogaster* has a large number of genes that are related to human disease genes, and it has already proven to be an effective tool for analysing the function of these genes and discovering novel genes involved in disease processes such as developmental disorders, neurological diseases, cancer, and so on. Although it is unfortunate that *D. melanogaster* will not always be a perfect model for human disease processes. In the future, determining which genes contribute to complex illnesses will likely

be a major priority in human genetics, and flies will once again provide a strong tool for identifying such interacting partners and understanding the processes that underpin such interconnections.

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