***Review Article***

***Drosophila Melanogaster* as a Substitute Model Organism for Autism Spectrum Disorder**

**ABSTRACT**

The surge in the prevalence of neurodevelopmental conditions including Autism Spectrum Disorder; a Disarray typically defined by a wide variety of conditions marked by difficulties in social skills, repetitive behaviors, disorganized speech, and challenges with nonverbal communication has increased the quest to elucidate its underlying mechanisms and create effective treatments by maximizing different animal models.

In recent decades, animal studies on autism spectrum disorder maximizing different animal models have increased. Despite the number of animal models in these findings, lasting alleviating measures have not been actualized, the known animal models are also associated with several limitations such as being too expensive, too unwieldy to handle, and characterized by a prolonged reproductive cycle, while in some areas of the world, they are becoming harder to acquire. In this regard, research is now focusing on the need to search for animal models unaffected by the stated limitations associated with the well-known animal models. *Drosophilia* *Melanogaster* (fruit fly) as a model organism in neurodegenerative, and neurodevelopmental diseases have been used by a few studies.   This review examines the limitations of the established animal models while highlighting the significance of fruit flies as a more effective model for studying ASD.

**Keywords:** Animal model; Autism Spectrum Disorder; *Drosophila* *Melanogaster*; fruit fly; Neurodevelopmental Disease.

**INTRODUCTION**

Autism Spectrum Disorder (ASD) was coined in 1911 by a German psychologist, Eugen Bleuler, used to describe a symptom of one of the most severe cases of schizophrenia, a concept he also created.[**1]** ASD is a group of conditions related to the development of the brain, it refers to a broad range of conditions characterized by challenges with social skills, repetitive behaviors, disorganized speech, and nonverbal communication,[**2]** Autism Spectrum Disorder has been called quite some things, however, if there is one thing to understand, Autism Spectrum Disorder is not a disarray that can be treated; it does not just disappear or get cured. It is simply the way an autistic individual’s brain works and a part of their identity that would always remain in some form even if certain characteristics become more or less noticeable over time. ASD severity and manifestation vary from person to person as some identify as high-functioning autism and some are low-functioning.[**3]** Some can have good communication skills while some talk perfectly but avoid eye contact and others can say only a smattering of words.

According to the Centers for Disease Control (CDC) in the United States, ASD affects an estimated one in thirty-six children and one in forty-five adults, moreover, in sub-Saharan African countries, one in one hundred and forty-five children.[4] World Health Organization reported the prevalence of autism as one in every hundred individuals worldwide.[5] ASD has been known to pose a significant burden to life and social stigma on autistic individuals. In this regard, there is an increasing quest to search for a probable lasting preventive measure or advances in its treatments. A study by Schneider and Przewłocki evaluated the effects of valproic acid; an antiepileptic drug in the treatment of epilepsy in pregnant rats and reports an alteration in behavioral indices that mimics autistic-like behaviors in pups prenatally exposed to valproic acid. This suggests that treatment of mothers in the gestational period with some drugs or substances may contribute to the pathogenesis of Autism Spectrum Disorder in offspring. [6] Several studies have explored the effects of different substances, extracts, and drugs in alleviating symptoms of ASD using various animal models such as Wistar rats, [7] guinea pigs,[8] and rabbits,[9] among others. The current review evaluates the downsides of the well-established model in studying ASD while focusing on the significance of fruit flies as a better model in studies on Autism Spectrum Disorder.

**ETIOLOGY OF AUTISM SPECTRUM DISORDER**

Initial attempts to pinpoint the specific genes linked to autism spectrum disorder (ASD) were largely unsuccessful.[10] Just a few decades ago, only a few genes were identified, and these were primarily associated with complex genetic conditions like Fragile X, Rett's, and Down syndrome,[11] where ASD is one of many possible symptoms.[12] However, recent research has made significant progress with the increasing number of genes identified as contributing factors. [13’14].

Autism Spectrum Disorder (ASD) has been said to likely begin during early brain development, possibly as early as the prenatal period.[15] Subtle signs of the disorder, such as delays in motor skills or atypical social behaviors, can often be observed in infancy.[16] These early indicators suggest that early detection and intervention may be beneficial for individuals with ASD. Recent genetic research has identified several genes associated with ASD, providing insights into its biological underpinnings.[17] Our understanding of these genetic factors helps pinpoint the developmental stages where ASD may arise and suggests potential avenues for targeted interventions. Moreover, studies have also revealed the causes of autism are associated with environmental factors [18] and premature birth [19]

***DROSOPHILA MELANOGASTER* (FRUIT FLIES), AS A PREFERRED MODEL ORGANISM**

Various nomenclature has been assumed for *Drosophila melanogaster* (fruit fly) by different scientists, it was referred to as “Great and Mighty” by Michele Markstein, “Tiny fly, Big Impact” by Amos Abolaji [20] while we referred to it as “Small but Mighty”, you cannot but tell and feel how little yet very unique this fly must be. Away from popular belief, rodents, particularly the Wistar rats are not the only organisms that have been used in biomedical research, other animals such as pigs, frogs, cats, rabbits, and sheep have been popularly used.[21] Even though these animal models have been utilized for many years, their availability is almost becoming burdensome in some parts of the world as some consider them too costly, too large to manage, and have a lengthy reproductive cycle, while in certain regions of the world, they are becoming increasingly difficult to obtain. Despite these factors, biomedical research must continue to find alleviating measures for several trending diseases and disorders. Recently, researchers have been seeing a need for more available and handy animals with a similar genetic makeup as that of humans that can be used in different neurological diseases and disorders varying from Alzheimer’s disease, [21] Parkinson’s disease, [22] and Autism Spectrum Disorder,[23] among others. The remarkable outcome of these findings has now further encouraged researchers to proceed with the use of fruit flies as a model in neurodevelopmental disorders as seen in ASD. *Drosophila melanogaster* was introduced into biomedical research around the 1900s when Charles Woodworth started breeding them and in 1910 when Thomas Hunt Morgan set up his famous Fly Room at Columbia University.[24] The fruit flies became an organism of interest as it was discovered tohave about 75% human disease-causing genes making it a wonderful model organism[25] with its short reproductive span compared to other organism models as another advantage over the well-known animal models.[26] Over the years, more insights have been shared on several types of cancer,[27,28] diabetes,[29] and addiction,[30] using fruit flies. Nobel Prizes have been won by Scholars for their studies using fruit flies as a model for certain diseases.

**SUITABILITY OF *DROSOPHILA MELANOGASTER* AUTISM SPECTRUM DISORDER**

This tiny fly, often considered an annoyance in our kitchens, has evolved into a mighty organism in the hands of biomedical researchers and neuroscientists trying to understand the causes and possible ways to cure neurodegenerative and better understand neurodevelopmental disorders. The relevance of *Drosophila* in neurological studies particularly on Autism Spectrum Disorder may look absurd as it attracts some controversies that a mere fly cannot be utilized considering the behavioral involvement in ASD. However, these little flies have over time proven to be indispensable in understanding the neurobiology and genetic basis which is said to be a hallmark of Autism Spectrum Disorder.

*Drosophila melanogaster* is now considered a valuable and preferred model organism for studying autism spectrum disorder (ASD) due to its ease of genetic manipulation (Hodgkin *et al.,* 2019). Research using fruit flies has identified key genes associated with ASD, such as NRXN1, NLGN3, and CNTNAP2.[31] Mutations in these genes can lead to autism-like behaviors in flies, providing insights into their roles in human neural development and behavior. Moreover, studies have identified shared genetic pathways, like the mTOR signaling pathway,[32] implicated in ASD in *Drosophila* and humans.[33] Fragile X syndrome (FXS) is a neurodevelopmental disorder caused by mutations in the FMR1 gene, leading to intellectual disability and often Autism Spectrum Disorder. The *Drosophila melanogaster* model, with its single FMR1 ortholog dfmr1, has been instrumental in studying FX.[34] Mutations in dfmr1, similar to those in FMR1, result in various behavioral and neuronal defects in *Drosophila*.[35] These include synaptic overgrowth, altered synaptic transmission, memory deficits, and circadian rhythm disruptions, the phenotypes recapitulate many of the symptoms observed in FXS patients.[36]

Furthermore, neurobehavioral research suggests that the dopamine (DA) network plays a significant role in autism spectrum disorder.[37] Mutations in genes involved in DA signaling, such as the dopamine transporter (DAT) and synapsin 1 (STX1), have been linked to ASD. Studies have shown that imbalances in dopamine levels within specific brain circuits can lead to behaviors associated with autism spectrum disorder.[38] Additionally, enlarged DA-enriched brain regions, like the striatum, have been correlated with the severity of ASD.[39] Recent studies have identified mutations in the DAT gene (hDAT-T356M, hDAT-R51W) and the STX1A gene (STX1A-R26Q) that affect dopamine transport and lead to behavioral abnormalities. The stated mutations have been characterized in *Drosophila* models, demonstrating their impact on locomotion and response to amphetamine.[40] These findings highlight the importance of the dopamine network in ASD and suggest potential avenues for further research and therapeutic interventions.

The conservation of neurotransmitter systems between fruit flies and mammals makes it a valuable model organism for studying neurological functions and behaviors paralleling autism symptoms, such as social interaction deficits, repetitive behaviors, and sensory processing abnormalities.[41] The use of sophisticated tools such as Experimental Chambers,[42] Thermogenetic Methods, Micro-Scale Platforms, and Connectomics have been maximized in recent studies to evaluate and study these behaviors, enhancing understanding of autism mechanisms and potential interventions.[43] Brain mapping of the organism in question reveals a detailed connectome of its brain, identifying nearly 140,000 neurons and over 50 million synapses.[44] A comprehensive exploration of the connections and interactions between its neurons is crucial for understanding brain function and development. The fruit fly's relatively simple yet sophisticated brain structure makes it a valuable model for neurodevelopmental research, offering insights that can be translated to understanding human brain function and disorders.

**CONCLUSION**

Scientific findings into the behavioral indices, genetic makeups, and brain mapping of *Drosophila melanogaster* as a model organism in neurodegenerative diseases have contributed valuable insights into the genetic and molecular mechanisms of ASD. By continuing to explore the neurobiological underpinnings of this condition, researchers can identify potential targets for therapeutic intervention as a means to the end that ultimately reduces the burden of the disorder and improves the quality of life for autistic individuals. While these findings offer valuable information, it is important to consider a possible means of translating fly research into clinical trials.

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