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Carbon quantum dots as emerging neuroprotective nanobiomaterials: Insights from *Drosophila melanogaster*

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Abstract: Many disciplines are becoming interested in the fascinating subjects of nanoscience and nanotechnology. Organic nanomaterials, especially carbon quantum dots (CQDs), have drawn a lot of curiosity in the field of nanotechnology due to their exceptional qualities. Research in a variety of scientific fields has focused on CQDs because of their distinctive qualities and wide range of uses, including neuromedicine. Recent research has demonstrated their application for neuroprotection, particularly through enhanced neuronal survival, modulation of neuroinflammatory pathways, and antioxidant activity. The modelling of disease pathophysiology and the identification of therapeutic intervention areas have advanced significantly. *Drosophila* has played a significant role in medication development for numerous aspects of human health during the past few decades. These concepts lay the groundwork for the use of flies in future studies on neurodevelopmental and neurodegenerative illnesses in order to obtain a deeper understanding of molecular pathways. This review systematically discusses the CQDs as a powerful nanotheranostic tool for the targeting and therapy of neurological disorders. This review also emphasis *in vivo* findings from *Drosophila* as a disease model for assessing neurotherapeutic efficacy as a disease model.

Index Terms - *Drosophila melanogaster*; carbon quantum dots; nanobiomaterials; neurodegeneration; neuroprotection; oxidative stress.

I. INTRODUCTION

Since neurodegenerative disorders (NDs) are typically linked to aging, their worldwide health burden represents a significant issue in today's society. NDs are terrible disorders that have a significant effect on human health and cause serious impairments and, eventually, death. The fact that NDs are incurable and that current treatments are solely intended to alleviate symptoms or slow the disease's course is a significant issue, despite the tremendous efforts being made to provide light on the biology behind these diseases. As a result, it is critical and difficult to design novel therapeutic strategies to combat NDs (Solana-Manrique et al., 2019; Tello et al., 2022). Issues such as low drug solubility, restricted bioavailability, ineffective blood–brain barrier (BBB) crossing limit the effective therapeutic approaches in NDs despite decades of research (Dugger & Dickson, 2017).

Carbon Quantum Dots (CQDs) are a unique carbon allotrope among organic nanomaterials have a lot of potential for therapeutic uses in drug delivery, gene therapy, bioimaging, and neurological disease treatment. Following Xu et al.'s 2004 accidental discovery of CQDs during the purification of single-layered carbon nanotubes, more research was conducted to examine their fluorescence characteristics and create a novel class of functional fluorescent nanomaterials (Kohli & Parab, 2025). Targeted delivery systems that can pass through biological barriers like the blood-brain barrier are made possible by their small size, low toxicity, and adaptable surface chemistry (Bhatia et al., 2025; Li et al., 2022). Because of their distinct physicochemical and biological characteristics, CQDs have become extremely attractive nanomaterials for the diagnosis and therapy of neurodegenerative illnesses and brain malignancies. Excessive ROS generation causes mitochondrial malfunction, lipid peroxidation, DNA damage, and neuronal death in diseases such as multiple sclerosis, Parkinson's disease, Alzheimer's disease and traumatic brain injury. CDs with anti-inflammatory and antioxidant qualities have great potential for treating CNS disorders marked by persistent neuroinflammation and oxidative stress. Their potential as theranostic agents for treating CNS disorders marked by persistent neuroinflammation and oxidative stress is further enhanced by their antioxidant, anti-inflammatory, photothermal, and photodynamic therapeutic qualities (Girma et al., 2026; Nisha et al., 2024; Zhang et al., 2025).

In order to understand the pathophysiology underlying these diseases, pertinent aspects of the disease must be modelled in a system that permits the proper level of simplification and has affordable costs and convenience without sacrificing the significance of the results. The evolutionary proximity of an organism to humans and the effectiveness with which they can be handled, manipulated, and investigated determine the benefits and drawbacks different models can offer. The intricate nature of the organism's central nervous system (CNS) is additional crucial factor to take into account in scientific studies of neurodegeneration in particularly (Lambrechts et al., 2017). Various *in vivo* and *in vitro* studies have investigated the carbon quantum dots in *Drosophila melanogaster* model for their toxicity, neurological and developmental effects (*A Systematic Analysis of Human Disease-Associated Gene Sequences In Drosophila Melanogaster - PMC*, n.d.; S. R. Mishra et al., 2024; Ugur et al., 2016). Research has shown that it is possible to deliver CQDs through meal exposure, which enables effective assessment of their physiological effects, absorption, and biodistribution (Chahal et al., 2024).

Moreover, *Drosophila* models of neurodegenerative disorders provide a whole-organism setting to evaluate the neuroprotective effectiveness of CQDs (Bilen & Bonini, 2005; Lu & Vogel, 2009). Behavioural experiments, molecular investigations, and genetic methods in *Drosophila* provide a platform to thoroughgoingly assess the CQD-mediated effects on neuronal function and survival (Pandey & Nichols, 2011). These investigations are crucial for improving our comprehension of CQD interactions in intricate biological systems and for directing their translational use (Molaei, 2019; Papanikolopoulou et al., 2019).

2. Carbon Quantum Dots: Synthesis and Physicochemical Properties

2.1 Synthesis Approaches

CQDs can be produced using a variety of synthetic techniques that fall into two categories: top-down and bottom-up (*Fluorescent Carbon Quantum Dots with Controllable Physicochemical Properties Fantastic for Emerging Applications: A Review - You - 2024 - Carbon Neutralization - Wiley Online Library*, n.d.; Lim et al., 2015; Molaei, 2019). The top-down approach uses techniques like arc discharge, laser ablation, and electrochemical oxidation to break down bigger carbon structures like nanodiamonds, graphite, carbon nanotubes, carbon soot, activated carbon, and graphite oxide. When purifying SWCNTs from arc-discharged soot, Xu et al. found the first instance of fluorescent CQDs. Conversely, the "bottom-up" methods use assisted synthetic and microwave synthetic processes to create CQDs from molecular precursors such citrate, polysaccharides, and polymer-silica nanocomposites. Because of their affordability, scalability, and capacity to regulate particle size and surface functionality, bottom-up approaches are frequently adopted. Green synthetic methods were introduced recently and these environmentally friendly methods eliminated the need for costly materials and complex experimental setups, allowing for the one-step production of CQDs (Bhatia et al., 2025; Lim et al., 2015; Molaei, 2019). To make the production of CQDs easier, a number of synthesis pathways involving both physical and chemical techniques have been devised (Singh et al., 2024).

2.2 Structural and Optical Properties

CQDs have special optical characteristics, such as excellent photostability and excitation-dependent photoluminescence. Their surface states affect biological activity and fluorescence behavior, while their nanoscale size promotes cellular uptake and interaction with biomolecules. CQDs have a unique core-shell structure that results from a nucleation process in which a self-passivated shell made up of several functional groups develops after a core gradually grows (Molaei, 2019; Siddhardha et al., 2020). The occurrence and distribution of functional groups on the surface of CQDs are also significantly influenced by the synthesis method and conditions (Molaei, 2019). CQDs exhibit a number of benefits in applications, including low toxicity, outstanding biocompatibility, easy functionalization and modification, good solubility in a variety of mediums, plenty in sources, and tunable fluorescence. These intriguing characteristics, along with their ease of synthesis, make CQDs a very potential photoluminescent (PL) tag substitute for the commonly employed inorganic semiconductor quantum dots (QDs) in biomedical applications (*Fluorescent Carbon Quantum Dots with Controllable Physicochemical Properties Fantastic for Emerging Applications: A Review - You - 2024 - Carbon Neutralization - Wiley Online Library*, n.d.).

3. *Drosophila melanogaster* as a Model for Nanoneurobiology

3.1 Advantages of the Model System genetics

Compared to rodent models, *Drosophila* has a number of benefits, such as ease of handling, a short life cycle, high fecundity, and a large number of offspring per generation. At 25°C, a single fertile mating pair can create hundreds of genetically identical progeny in ten to twelve days. In contrast, only a few pups are produced every three to four months in conventional rodent models (De Lazzari et al., 2020; Kashyap et al., 2023; Panchal & Tiwari, 2017; Pandey & Nichols, 2011; Papanikolopoulou et al., 2019). Also, with just four pairs of chromosomes, flies are easily genetically modified. Additionally, fruit flies are simple to cultivate and work with in the lab, and creating fly mutant strains is now comparatively simple. All of these factors have made genetic research easier, even those that need for the creation of particular fly lines or large numbers of individuals for robust statistical analysis (De Lazzari et al., 2020; Pandey & Nichols, 2011).

One viable substitute in the drug discovery process is the fruit fly *Drosophila melanogaster*. With just three chromosomes carrying the majority of the genome, the fly genome has been fully sequenced and annotated, encoding for slightly over 14,000 genes. Fly and mammal homologs typically have an overall identity of about 40% at the nucleotide or protein sequence level; but, in conserved functional domains, it can reach 80–90% or more (Pandey & Nichols, 2011). Flies and mammals share many physiological and developmental pathways, and flies have functional homologues for around 75% of human disease genes (Şentürk & Bellen, 2018). Despite the fact that humans and flies differ greatly, the degree of biology and physiology conservation makes *D. melanogaster* a very useful tool for finding new drugs (Pandey & Nichols, 2011). The effects of the targeted substances can be investigated in flies (diseased model) by feeding them targeted compound containing diet and then looking at developmental changes and phenotypic alterations (eye, any anomalies, etc.) (Panchal & Tiwari, 2017).

3.2 Nervous System and Relevance

Because *Drosophila* has a sophisticated nerve system, the Central Nerve System (CNS), which is comparable to higher species, it has greatly advanced our understanding of neurobiology. Subsequently, the *Drosophila* brain is described as having over 250,000 neurons that use a variety of neurotransmitters similar to those found in human neurons (Lambrechts et al., 2017). The 100,000 neurons that make up the *Drosophila* nervous system create intricate neuronal circuits and neuropiles, which are in responsible for fly activities including phototaxis and locomotion (Panchal & Tiwari, 2017). Mammals and flies share several neuromodulator peptides, biogenic amines like dopamine and serotonin, and the same neurotransmitters (GABA, glutamate, and acetylcholine). Similar to mammals, action potentials are propagated by sodium channels in flies, and membrane potential is controlled by the same families of potassium and calcium channels. Information is transferred between neurons in both systems at specific areas of contact known as synapses, which share a protein organization. Therefore, knowledge gained about the nervous system in *Drosophila* is frequently applicable to other species (Venken et al., 2011).

The most advanced *in vivo* modifications to address the function of neurons and neuronally expressed genes are currently possible in *Drosophila*, the eukaryotic model organism. The development of the

nervous system, growth cone guidance and target recognition, exocytosis and endocytosis at synapses, synapse remodelling, and the neural circuitry underlying behaviours like courtship, sleep and diurnal rhythms, aggression, learning, and memory have all been better understood owing to research on *Drosophila* (Venken et al., 2011). Furthermore, it is now clear that *Drosophila* is a useful model organism for studying genes related to human disease, particularly neurodegenerative mechanisms linked to Parkinson's disease, Alzheimer's disease, polyglutamine and other triplet repeat expansion diseases, amyotrophic lateral sclerosis, or neurological conditions like schizophrenia, depression, and epilepsy (Lu & Vogel, 2009; Venken et al., 2011).

Over the past 20 years neurological dysfunction, such as neurodegeneration, epilepsy, dementias, stroke, traumatic brain injury, and brain tumours, has been more frequently modelled in *Drosophila* (Ugur et al., 2016). One important pathological finding linked to a number of neurological conditions, such as AD, PD, ALS, and prion diseases, is the accumulation of harmful proteins in inclusions or aggregates. These could result in harmful aggregates or changed protein function, which protein overexpression frequently mimics. The most popular method for overexpressing genes in flies is based on the GAL4/UAS-mediated binary expression system, which models neurodegenerative and neurodevelopmental conditions employing drivers unique to tissue and neuronal subtypes (Panchal & Tiwari, 2017; Papanikolopoulou et al., 2019; Şentürk & Bellen, 2018). Translational insights into neurodegenerative illnesses are made possible by the structural and functional similarities between the neural systems of *Drosophila* and mammals.

3.3 Behavioural and Molecular Assays

One of the most well-known organisms used in genetic, developmental, behavioural, and molecular/biochemical research is *Drosophila*. It is possible to score and measure a neurodegenerative impairment in fly using a number of different assays (Lambrechts et al., 2017; McGurk et al., 2015; Panchal & Tiwari, 2017). Locomotor activity, lifespan analysis, feeding behavior, and oxidative stress indicators are common assays that offer a thorough assessment of the impacts of nanomaterials. Developmental assays make it possible to assess how medications affect *Drosophila* development *in vivo*, which is frequently affected in neurodegenerative models. Lifespan analysis in adult flies is one of the most popular developmental experiments (Solana-Manrique et al., 2019).

To study *Drosophila* models of neurodegenerative diseases, behavioural assays are very helpful. Progressive loss of locomotor abilities which is one of the most common symptoms associated with human NDs such as PD or AD can be easily evaluated in vivo in the *Drosophila* models (Lambrechts et al., 2017; McGurk et al., 2015; Panchal & Tiwari, 2017). The larval crawling assay, which can be carried out with model larvae either with or without a potential medication, is the most popular method for examining locomotor activity in third instar larvae (Pandey & Nichols, 2011). The climbing assay, also called the negative geotaxis assay, which is based on innate tendency of flies to move against gravity when tapped to the bottom of an empty vial, makes it simple to examine locomotor activity in adult flies (Solana-Manrique et al., 2019). Neurodegenerative diseases affect nervous system by causing loss of neurons and damage to specific regions. Neuronal degeneration is thought to be caused by a number of

processes, including as oxidative stress (OS), inflammation, and mitochondrial malfunction. Determining the levels of ROS, H_2O_2, malondyaldehide (a diagnostic of lipid peroxidation), and protein carbonyl content (a marker of protein oxidation) are the most often used assays to investigate OS indicators. Using several commercial kits, they can all be quantified in *Drosophila* with ease (Solana-Manrique et al., 2019).

4. Mechanisms of Neuroprotection by CQDs: Insights from *Drosophila* studies

Through a variety of mechanisms, such as ROS scavenging, inflammatory regulation, apoptosis suppression, and neurogenesis stimulation, CQDs have neuroprotective effects (M. Mishra & Panda, 2021; Zhang et al., 2025). In *Drosophila*, CQDs given by diet show effective absorption and distribution, especially in the gut and brain regions (Chahal et al., 2024). A study analysed the remediated and non-remediated real wastewater for their comparative toxicity. *Drosophila melanogaster* was utilized to assess the toxicity of amin-rich CQDs (A-CQDs) treated real wastewater by performing toxicity tests. A-CQD significantly improved the eclosion efficiency and negative geotaxis behaviour in flies treated across varying wastewater concentrations. Additionally, the A-CQD-remediated wastewater-treated groups had less abnormal features in all life stages, according to the total anomaly score analysis. The findings of the investigation show that A-CQD can significantly lower the toxicity of wastewater contaminated with dyes, indicating its potential as a successful treatment technique and that the treated sample was safe for human health, agriculture, and the environment (Meena et al., 2024).

Another study used a novel nontoxic and fluorescent polyelectrolyte carbon quantum dots (PECQDs), synthesized from waste plant materials, to display *in vivo* images of several internal organs and life cycle stages of *Drosophila melanogaster*. PECQDs after their dietary intake in *Drosophila melanogaster* provided a new approach for imaging live specimens. *Drosophila* were exposed to 1 ppm of soluble carbon quantum dots for 12 hours, which allowed for fluorescence microscopy imaging of their non-invasive internal organs at various developmental stages without any discernible harmful consequences. the present study we show the in vivo images of different life cycle stages and various internal organs of Drosophila melanogaster using a new fluorescent material like PECQDs. Results suggested that it may be possible to directly assess the effectiveness of therapeutic treatments without the need for intrusive procedures by using a fluorescent probe to visualize interior organs in living cells (Parvin et al., 2013).

A multifunctional nanomaterial that combines antioxidant qualities, photothermal conversion capacity, and Cu2+ chelating ability for multi-targeted treatment of AD was effectively created in a study by Zhang et al. By scavenging free radicals and controlling enzyme activity, exceptional antioxidant qualities of selenium can significantly reduce oxidative stress under pathological settings, according to in vitro investigations. Because elemental selenium has a restricted safety threshold, doping carbon quantum dots with selenium was thought to boost the material's antioxidant capability and enhance its safety and multifunctional therapeutic effect for AD. In contrast to typical selenium nanoparticles (SeNPs), selenium-doped carbon quantum dots (SeCQDs) maintain their capacity for photothermal conversion while also having good biocompatibility and dispersion. To improve the therapeutic impact, the design

can make optimal use of the material's dual properties as a Cu2+ chelator and a photothermal agent to prevent Aβ deposition and remove excessive reactive oxygen species (Zhang et al., 2025).

Traumatic spinal cord injury (TSCI) causes excess production of reactive oxygen species (ROS) which has been identified as a leading cause of secondary injury. In a study, it was shown that selenium-doped carbon quantum dots (Se-CQDs), which have the capacity to scavenge reactive oxygen species, had good biocompatibility and a notable protective impact against oxidative damage caused by H2O2 in astrocytes and PC12 cells. Additionally, Se-CQDs demonstrated strong anti-inflammatory and anti-apoptotic properties, which decreased the development of glial scars and improved the in vivo survival of neurons with intact myelin sheaths. Consequently, the locomotor function of rats with TSCI was significantly improved by Se-CQDs (Luo et al., 2020).

Another study uses *Drosophila melanogaster* as an epileptic model to examine the possible impacts of carbon dots generated from Martynia annua (MA-CDs). In flies treated with both MA-CDs and antiepileptic drug Carbamazepine (CBZ), seizures caused by heat shock and vortex were considerably reduced in a dose-dependent manner. Higher dosages of CBZ and MA-CDs, however, improved the flies' capacity to climb up. Higher doses of CBZ enhanced memory and learning in mutant flies in cognitive tests, while MA-CDs also had a notable effect (Abbigeri et al., 2025).

Another study assessed the neuroprotective effect of carbon quantum dots produced from citric acid (Cit-CQDs) on human neuroblastoma-derived SH-SY5Y cell lines and a nematode exposed to paraquat (*Caenorhabditis elegans*). The findings showed that Cit-CQDs can reduce paraquat-induced elevated reactive oxygen species (ROS) levels in SH-SY5Y cells and scavenge free radicals in test tube assays. This suggests that Cit-CQDs provide neuroprotection for cell lines and organisms against xenotoxicant-associated neuronal injury and death. The work proposes Cit-CQDs as a biobased, green chemistry-synthesised nanomaterial that may be useful for treating neurodegenerative diseases (Henriquez et al., 2022).

Ahlawat et al. showed that sustainable carbon quantum dots (CQDs) formed from gelatin produced by green chemistry reduce the neurotoxic effects of paraquat and the subsequent reduction in organismal mortality. In paraquat-insulted neuroblastoma-derived SHSY-5Y cells, gelatin-derived CQDs were shown to have antioxidant qualities and reduced ROS increase, shielding the cells from herbicide-induced cell death (Ahlawat et al., 2022).

5. Conclusion and future perspectives

In the last ten years, CQDs- a novel class of nanomaterials have garnered a lot of interest and a new age in biomedicine has begun with the development of CQD research. In the context of *in vivo* biomedical applications, superior chemical and photochemical stability as well as chemically non-toxic chemistry of CQDs provide a distinct benefit. Owing to the conservation in multiple molecular and cellular pathways between flies and mammals *Drosophila* models are appreciated for their potential contributions in biomedical field. The significance of *Drosophila* in the analysis of neurodegenerative diseases is demonstrated by the findings offered in the past several years, that were subsequently translated to more

intricate model organisms and, in certain situations, approached clinical application. The area of disease-specific modelling of neurodegenerative diseases in *Drosophila* is presently thriving, and new discoveries can be easily applied to more traditional systems and, in certain situations. In the years ahead, *Drosophila* will be at the center of new breakthroughs with regard to the pathophysiology and treatment of neurodegenerative disorders due to its ease of study, manipulation, and screening.

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