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Caenorhabditis elegans as a model system to evaluate neuroprotective potential of nano formulations

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The impact of neurodegenerative illnesses on society is significant, but the mechanisms leading to neuronal malfunction and death in these conditions remain largely unknown despite identifying essential disease genes. To pinpoint the mechanisms behind the pathophysiology of neurodegenerative diseases, several researchers have turned to nematode *C. elegans* instead of using mammals. Since *C. elegans* is transparent, free-living, and amenable to culture, it has several benefits. As a result, all the neurons in *C. elegans* can be easily identified, and their connections are understood. Human proteins linked to Neurodegeneration can be made to express in them. It is also possible to analyze how *C. elegans* orthologs of the genes responsible for human neurodegenerative diseases function. In this article, we focused at some of the most important *C. elegans* neurodegeneration models that accurately represent many elements of human neurodegenerative illness. It has been observed that studies using the adaptable *C. elegans* have helped us in better understanding of human diseases. These studies have used it to replicate several aspects of human neurodegeneration. A nanotech approach involves engineering materials or equipments interacting with biological systems at the molecular level to trigger physiological responses by increasing stimulation, responding, and interacting with target sites while minimizing side effects, thus revolutionizing the treatment and diagnosis of neurodegenerative diseases. Nanotechnologies are being used to treat neurological disorders and deliver nanoscale drugs. This review explores the current and future uses of these nanotechnologies as innovative therapeutic modalities in treatment of neurodegenerative diseases using *C elegans* as an experimental model.

KEYWORDS

Alzheimer's disease, amyotrophic lateral scelerosis, *C. elegans*, Huntington's disease, Parkinson's disease, nanotechnology, neurodegeneration

Introduction

Various model systems are being used to understand the genesis and progression of human diseases. Better understanding is needful in drug screening/development. Humans would undoubtedly be the finest study subjects, but this is typically not the case due to practical and moral/ethical considerations. Other mammals are the next apparent option and are good in many aspects, mainly when emulating behavioral characteristics. Various

mammalian models, including rodents, are critically established to understand the pathophysiology and to explore new therapeutic interventions for neurodegenerative disorders (NDs) because of their ability to mimic various clinical features like neuronal loss, alteration in neuronal signaling and transmission, motor and non-motor dysfunctions (Torres and Dunnett, 2011; Thiele et al., 2012; Ribeiro et al., 2013; Schirinzi et al., 2016). But, several toxin-induced ND models in mammals still fail to mimic many pathological hallmarks like gross morphological transformation and steady neurodegenerative progression (Ribeiro et al., 2013; Schirinzi et al., 2016; Visanji et al., 2016). However, they also have few other significant drawbacks, including how well they imitate particular disease, the sluggish pathological development, and the length of time needed to conclude. To better understand these pathological hallmarks in ND and overcome the limitations of well-established rodent models, numerous invertebrate models like those of the *Drosophila melanogaster* or *Caenorhabditis elegans* has gained popularity recently and are being developed as first-round preclinical investigation followed by mammalian assay (Brenner, 1974; Sulston et al., 1975).

C. elegans is an effective tool for development of different experimental models because of its various characteristics and simple culturing/maintenance. This free-living, tiny, non-lethal, 1 mm long self-fertile hermaphrodite nematode has a 3.5-day reproduction cycle with survival at 20°C for roughly 3 weeks. It typically grows in the soil but can easily be raised in a lab environment on *Escherichia coli* diet (Garigan et al., 2002; Olsen et al., 2006; Chew et al., 2017). *C. elegans* share similar cellular mechanisms and pathways to humans and other mammals, which can be genetically analyzed and studied using RNA interference technologies (Fire et al., 1998), Furthermore, ease of its laboratory preservation, transparent anatomical observation body, high genetic homology (60–80%) to humans, complete genetic sequence detection, stored biological cell responses, high fertility rates (240 eggs/worm in a few days), and access to cellular biological tools (such as transgenic, gene knockouts) makes *C. elegans* a considerable invertebrate model for NDs and its associated genetic research over fundamental ND neurobehavioral studies (Matsunami, 2018; Youssef et al., 2019). *C. elegans* is also considered as an advanced model of biology in the study of aging. Apart from a few anatomical variations from mammals, the nervous system of the *C. elegans* embraces a circumpharyngeal nerve ring, along with neurotransmitter systems for acetylcholine (ACh), glutamate, dopamine (DA), and gamma-aminobutyric acid (GABA), including their receptor and synaptic features, like that of primary cellular and molecular features in mammalian neurons (Markaki and Tavernarakis, 2010; Maulik et al., 2017). The nervous system of nematodes contains 302 neurons in adult female hermaphrodites while 383 in males. More than 7,600 synapses are formed by 118 morphologically different classes and 56 glia cells (White et al., 1986; Bargmann, 1998; Barclay et al., 2012). Alzheimer's disease (AD), Parkinson's disease (PD), Amyotrophic lateral sclerosis (ALS), and Huntington's disease (HD) are the few major NDs that have been modeled using *C. elegans* (Sattelle and Buckingham, 2006; Kim et al., 2019).

Furthermore, the use of a nanoparticulated drug delivery system is a cutting-edge technology that is widely employed to transport medications right to the brain, and has been proven to be incredibly effective in treating various CNS illnesses. Nano-sized particles have attracted great interest because of their capacity to stop chemical and enzymatic drug degradation. These nano drugs also improve drug solubility and ease drug transport across biological membranes *via* direct drug delivery to the site of action, which consequently minimize drug side effects and raise its therapeutic index. Various nanoparticulate systems including polymeric nanoparticles, nanoemulsions, liposomes, *etc.* have been developed so far that opened up new possibilities beyond simply enhancing traditional treatments' pharmacokinetics (Wadhwa et al., 2022). Nanomaterial toxicity is a growing concern in nanotechnology as more and more nanomaterials are produced and used in a variety of applications. Due to their strong antibacterial action, Silver nanoparticles (AgNPs) are one of the most popular commercial nanomaterials at the moment (Durán et al., 2016). AgNPs' toxicity has been proven in numerous models over the years, including bacteria (Xiu et al., 2012), cell culture systems (Wang et al., 2013), zebrafish (Rahman et al., 2009), and mice (Maurer et al., 2016). Due to its unique characteristics, *C. elegans* is quickly becoming one of the most valuable model systems for determining the potential toxicity of nanoparticles. Due to the absence of established protocols, there have been a number of difficulties up until this point. Consideration must be taken seriously to improve the experimental settings for nanotoxicity to get reliable and accurate results (Roh et al., 2009; Maurer et al., 2016). Thus, the present manuscript highlights the current research that endeavored *C. elegans* as a promising screening model to underline the pathogenecity of NDs and associated molecular mechanism of therapeutic inventions that can be used for the treatments of various NDs, with a special attention to the implementation of these *C. elegans* models in nanomedicine and nanotechnology.

Neurodegenerative diseases and *C. elegans* models

Researches affirmed that several NDs have a significant genetic influence, and is particularly true of familial forms of these diseases, where genetics plays a more critical role in disease pathology. The central part of *C. elegans* research on NDs has been devoted to understand the effects of genes involved in AD, PD, ALS, and HD. Most mutations in these genes associated with the diseases are autosomal dominant mutations, since one copy

of each mutation causes disease (White et al., 1986; Chalfie et al., 1994). *C. elegans* may be treated as advanced model of biology in the study of neurodegeneration associated with different diseases. Apart from above discussed advantages, the short lifespan (about 3 weeks) and small size of this organism reduce experimental cost, and can be used for high-throughput screening studies, which is advantageous to screen neuroprotective nanoformulations/drugs. Also, no ethical consideration and requirements with experimentations will led to many breakthrough discoveries in the field of neuroprotective and aging research using *C. elegans* (David et al., 2010).

C. elegans models for Alzheimer's disease

Alzheimer's disease (AD) is the most common form of dementia, characterized by amyloid plaque formation through β-secretase and γ-secretes enzymes and hyperphosphorylation of tau protein. Frontotemporal dementia is a distinct neurodegenerative condition caused by mutations in the tau gene, while *presenilin* mutation causes familiar forms of the disease. Amyloid precursor protein (APP) gene is a crucial factor for AD that helps in the cleavage of the amyloid peptide. *C. elegans* has an APP orthologous *APL-1*, but this protein lacks the amyloid peptide. Additionally, nematodes' genome does not contain these β-Secretase cleaving enzymes. Human peptide expression in the worms has always been used to create *elegans* models of amyloid Aβ toxicity. By producing the Aβ-42 peptide in body-wall muscle, the first *C. elegans* model of a ND was created (Link, 1995; Alexander et al., 2014). As a result, transgenic worms suffer from paralysis, and amyloid peptide accumulation was observed in their muscles. Many models in worms were developed to investigate the neuroprotective effects of herbal drugs and many synthetic compounds. To test the neuron activity of compounds worm models with either muscle or neuronal Aβ-42 expression have since been developed (Li and Le, 2013; Alexander et al., 2014; Ma et al., 2018).

Notably in 1993, the first gene, *presenilin,* was identified in *C. elegans*, which later on found linked with early-onset (Levitan et al., 1996; De Strooper et al., 1999; Wittenburg et al., 2000). In *C. elegans* three *presenilin* genes i.e. *sel-12, hop-1, and spe-4* have been found, among which *Hop-1 and sel-12* are broadly expressed, whereas, *spe-4* is only displayed in the male germ line (Calahorro and Ruiz-Rubio, 2011; Alexander et al., 2014; Sarasija and Norman, 2018). Furthermore, higher sequence similarity to the human *presenilins* gene, which controls APP processing, can be seen in sel-12. *APL-1* overexpression results in 70% mortality, which is reversed in *sel-12* mutants, suggesting that *Sel-12* regulates *APL-1* cleavage. Due to the dysregulation of mitochondrial calcium (Ca^{2+}) homeostasis caused by *sel-12* mutations, the worms develop AD (Sarasija et al., 2018; Sarasija and Norman, 2018). Only *ptl-1*, an orthologue of tau with significant sequence similarity to mammalian tau, is present in *C. elegans* (shown in Figure 1). There is proof that human tau and *ptl-1* both play crucial roles in preserving the integrity of the nervous system. Tau mutations cause frontotemporal dementia, and increasing uncoordinated phenotypes and Neurodegeneration are produced in worm models by transgenic production of human tau variations (Alexander et al., 2014; Pir et al., 2017).

The effects of chondroitin sulfate E on neuronal adhesion, neurite outgrowth, and neuroprotection are regulated. Chondroitin sulfate E prevents amyloid peptide from aggregating and causing toxicity in transgenic *C. elegans*, according to a research (Wang et al., 2022). In a different study, transgenic *C. elegans* producing amyloid genic proteins are treated with silver nanoparticles. The *C. elegans* strains such as CL2120 and CPV10, which express the human b2-microglobulin (b2-m) and the Ab3-42 peptide, respectively, simulate illnesses related to the deposition of amyloid, one of the most significant categories of chronic disorders linked to population aging. As a result, silver nanoparticles' toxicity on several physiological parameters in both *C. elegans* in the wild type and in transgenic form was established. The sensitivity of the tests conducted on the worms was compared to that produced from the well-established human brain D384 and lung A549 cell lines (Diomede et al., 2012; Wang et al., 2022).

C. elegans β-amyloid peptide models

It is hypothesized that the accumulation of β-amyloid causes AD, therefore, by expressing human Aβ peptide constructs in worm muscle cells, numerous transgenic strains of *C. elegans* can be developed for underlining the pathogenesis of AD (Link, 1995). Treusch et al. (2011) have discovered many neurodegenerative modifiers that are functionally linked to cytoskeleton genes (*YAP 1802, INP52, SLA1, CRM1, GRR1, KEM1,* and *RTS1*). In 1995, the first *C. elegans* transgenic model CL2006 was developed by expressing human Aβ1-42 in body-wall muscle using the unc-54 promoter, which is widely employed nowadays to illustrate the neuroprotective properties of various natural and synthetic compounds (Link, 1995). Two 8-OHQs, PBT2, and clioquinol, which were earlier, found to have neuroprotective effects in mice models of AD, also demonstrated effective in treating Aβ-42 toxicity in neurons and body wall muscle cells of *C. elegans* (Mccoll et al., 2012; Matlack et al., 2014). Currently, three types of *C. elegans* models for AD such as *unc-54, myo-3, and snb-1* are widely employed for screening neuroprotective effect of drug against Aβ toxicity.

Due to age-dependent paralysis in CL2006 *C. elegans*, it is difficult to explain whether protective compounds are altering Aβ peptide toxicity or aging (Cohen et al., 2006) Several myo-3 promoters have been added to *C. elegans* to overcome this constraint (Link et al., 2003). Dostal and Link (2010) reported

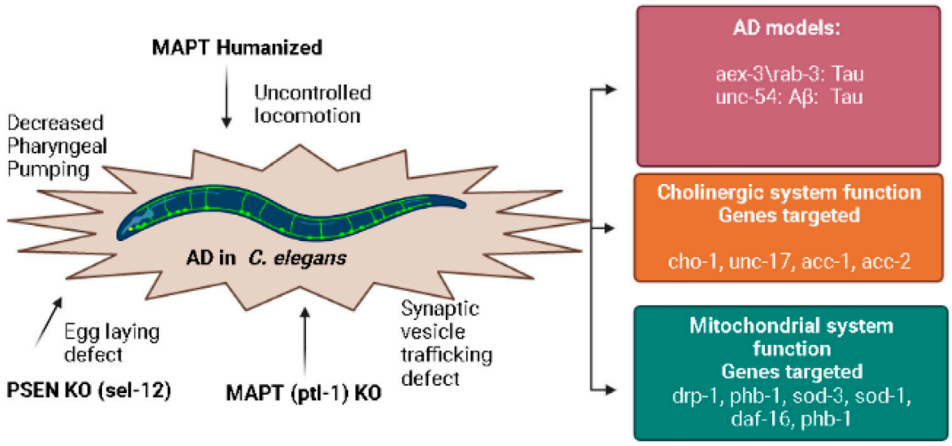

FIGURE 1
C. elegans models for Alzheimer's disease by targeting different genes.

that *CL4176* transgenic *C. elegans* paralyzes immediately, repeatedly, and completely at 25°C. Apart from paralysis, this model exhibits oxidative stress, Aβ deposits, and increased autophagy (Link et al., 2003; Florez-McClure et al., 2007). Muscle cells express Aβ in both types, but neuronal Aβ expression may better represent AD pathophysiology. Later on CL2355 strain was used as an AD model to examine the neuroprotective properties of seven new 2-aryl ethenyl quinoline derivatives. In addition to improving learning memory and suppressing Aβ monomer production, two of the seven chemicals decreased the stress response induced by Aβ in the *elegans* AD model (He et al., 2017).

C. elegans tauopathy models

AD is linked to the accumulation of NFT, which aggregates into insoluble hyperphosphorylated Tau protein (Mandelkow and Mandelkow, 1998). Several transgenic worms expressing Tau components have been developed to study the consequences of neuronal Tau expression (Kraemer et al., 2003; Miyasaka et al., 2005; Brandt et al., 2009). *Ptl-1* is the gene in *C. elegans* that is homologous to the tau protein. However, the *ptl-1* function deficiency cannot entirely imitate the clinical characteristic of tauopathy (Krieg et al., 2017). The neurons of *C. elegans* exhibit wild-type and frontal, temporal cognitive impairment with parkinson chromosome 17 type mutant human tau protein (Kraemer et al., 2003). It's interesting to note that frontotemporal dementia with parkinsonism chromosome 17 type (FTDP-17), a different neurodegenerative illness, appears to be caused by tau gene mutations rather than Alzheimer's disease (Rademakers et al., 2012). With age, insoluble phosphorylated tau protein deposition increases along with neuron loss and inconsistent movement (Liachko et al., 2016). When compared to non-transgenic *C. elegans*, the lifespan of axe-3/tau and *FTLD-17* mutant axe-3/tau was significantly reduced. The *C. elegans* axe-3/tau V337M strain was utilized for RNAi screening to find the abnormal phenotype brought on by tau protein (Kraemer et al., 2006). The mec-7/tau *C. elegans* mutants R406W and P301L express tau protein in tactual neurons, that consequently induces progressive loss of tactual sensibility with aging, however, neurons do not degenerate, instead, they acquire neuritic flaws, and gradually lose their functionality (Miyasaka et al., 2016). Furthermore, over expressing GSK-3 can make tau protein more toxic, over expressing HSP70 can only slightly lower tau protein toxicity (Miyasaka et al., 2005). Brandt et al. (2009) generated human tau and a pseudo hyperphosphorylated (PHP) tau pan-neuronal transgenic *C. elegans* model to investigate the role of phosphorylation in tau protein toxicity. As the animals grow older, both wild and PHP types suffer from identical mobility disorders. Tau protein aggregation only developed in PHP type, not wild type, but caused faulty motor neuron development .

According to Fatouros et al. (2012) these tau models also inhibit tau aggregation and aid in discovering substances that have neuroprotective action in the *C. elegans* model. Tetracycline, coffee extract (without caffeine), copper, and traditional Chinese medicine are substances that have demonstrated anti-aggregation protective properties (Li and Le, 2013). On the human Aβ transgenic worms, Link et al. (2003) used microarrays to analyze gene expression. They have discovered 240 down-regulated genes and 67 up-regulated genes. Transgenic worms exhibit strong induction of the transcript levels of B-crystallin (CRYAB) and tumor necrosis factor-induced protein 1. Postmortem AD brain tissue also indicates upregulation of the human homologs of the genes.

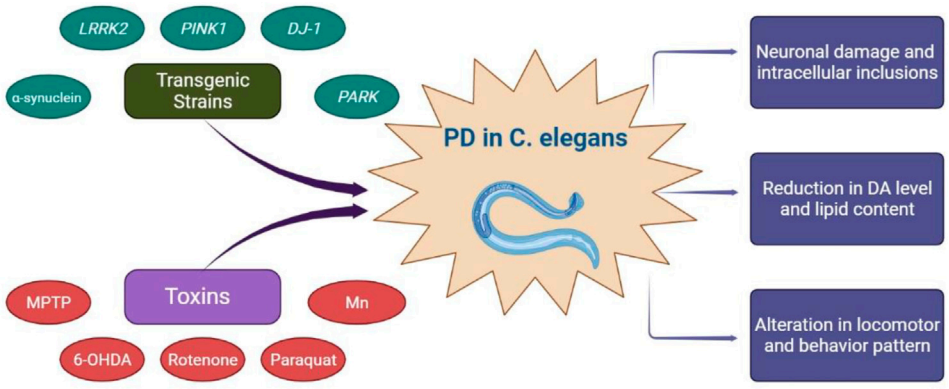

FIGURE 2
C. elegans models for Parkinson's disease and their pathological outcomes.

Noteworthy, a DA receptor antagonist antipsychotic, azaperon, used to treat schizophrenia, improve transgenic worm movement, and reduce the insoluble tau level in *C. elegans* AD model, indicating dopamine D2 receptor antagonism may be a promising method for preventing tau-induced neurotoxicity (McCormick et al., 2013).

C. elegans models for Parkinson's disease

Parkinson's disease is considered the second most rapidly growing neurological disorder affecting millions of lives and is now being intrigued as a burden to healthy life owing to its progression (Saewanee et al., 2021). Pathophysiologically, PD is pigeonholed by continuous loss of DA neurons with pervasive intracellular accumulation of the α-synuclein protein in the substantia nigra pars compacta causing irregularities in motor behavior (Thome et al., 2016; Ullah and Khan, 2018), and can be easily diagnosed with four significant clinical cardinal signs, i.e., rigidity, resting tremor, bradykinesia, and loss of postural reflexes (Maulik et al., 2017). Since DA neuronal loss affects both the central and peripheral nervous system, certain non-motor clinical features, including memory loss, depression, anxiety, dysphagia, sleep disorder, and adipsia, are also common in PD (Maulik et al., 2017; Saewanee et al., 2021). The etiology of PD is unclear, yet familial (genetic) and sporadic (environmental) are considered two principal factors triggering the development of PD, and involves predisposition of various genes like α-synuclein, *Parkin (PARK2), PTEN-induced putative kinase 1 (PINK1), ubiquitin C-terminal hydrolase L1(UCHL1), leucine-rich repeat kinase 2 (LRRK2), glucocerebrosidase (GBA), DJ-1, etc.* (Trinh and Farrer, 2013) (Figure 2). Noteworthy, these genes are at least present in one *C. elegans* homolog (Harrington et al., 2010; Chege and McColl, 2014; Lee and Cannon, 2015). Interestingly, hermaphroditic *C. elegans* consists of around 302 neurons, out of which eight are DA in nature, associated with four DA receptors and are homologs to mammalian DA system (Sulston et al., 1975; Chase and Koelle, 2007). Although, α-synuclein, which is responsible for DA neuronal degradation, is not endogenous to *C. elegans* (Lakso et al., 2003; Karpinar et al., 2009).

Genetic *C. elegans* models

C. elegans transgenic models are used to study the genetic basis of PD and its allied neuronal deficits. The α-Synuclein gene is one of the genes responsible for regulating several enzymes associated with DA transportation and release (Maulik et al., 2017). It is one of the significant causative genes for the PD, as any duplicate or triplication α-synuclein locus induces familial type PD (Van Ham et al., 2008). Several transgenic *C elegans* models with mammalian α-synuclein homologues have been generated to investigate the role of α-synuclein overexpression and aggregation in Parkinson's disease. (Maulik et al., 2017). *C. elegans* transgenic α-synuclein strains NL5901, having phenotype *unc-54p*:: α-synuclein::YFP + *unc-119* is widely employed to selectively underline the mechanism of new and potent anti-PD drugs (Jadiya et al., 2011; Bodhicharla et al., 2013; García-Moreno et al., 2019; Anjaneyulu et al., 2020; Chalorak et al., 2021; Schmidt et al., 2021). Anjaneyulu et al. (2020) explored the six ayurvedic nootropics extracts using NL5901 transgenic strain to understand their anti-PD and neuroprotective mechanisms. In addition, Wild isolate Bristol Type N2, OW13, and DDP1 are a few other transgenic strains, having α-synuclein overexpression as their pathological hallmark, which are also being used for understanding the pathogenesis of PD and for screening anti-PD drugs (Bodhicharla et al., 2013; Fu et al., 2014a; Fu et al., 2014b; Chen et al., 2015). Despite overexpressed wild-type α-synuclein

strains, mutant α-synuclein (A53T, E46K, and A30P) and α-synuclein pre-formed fibril transgenic strains are also extensively employed as PD transgenic models for *C. elegans* (Lakso et al., 2003; Maulik et al., 2017; Polinski et al., 2018; Zhang et al., 2018; Gaeta et al., 2019).

Mutations in the LRRK2 gene in human is also a prevalent cause of autosomal dominant and idiopathic PD, and its homologous gene, lrk-1, is present in *C. elegans* (Sämann et al., 2009; Liu et al., 2011; Cooper et al., 2017). Yao et al., 2010, developed transgenic LRRK2 *C. elegans* models by mutating R1441C/G and G2019S within GTPase and kinase domains, which later showed depletion in DA level, behavioral and locomotor dysfunction in worms due to over-expression of LRRK2 proteins (Yao et al., 2010). Similarly, mutation of *the PINK1 gene,* encoded as *pink-1* in *C. elegans*, portrayed a significant loss in dopamine-dependent behaviors in *C. elegans* along with age-dependent- mitochondrial dysfunction (Cooper et al., 2017). Deletion of djr-1.1, an ortholog of DJ-1 gene in *C. elegans*, can also impact dopamine-dependent behaviors with elevated sensitivity to oxidative stress (Cooper et al., 2017). Noteworthy, several neuronal transgenic strains such as BZ555, pRF4, BY200, and TG2435, tagged explicitly with a green fluorescent protein (GFP) and a DAT-1 promoter, have been used with environmental toxins to trigger PD in *C. elegans* (Masoudi et al., 2014).

Toxin-Induced Models

The neurotoxin 1-methyl-1, 2, 3, 6-tetrahydropyidine (MPTP) induced-PD model is one of the well-established and widely used screening models for the detection of potential anti-PD drugs in rodents which triggers PD-like symptoms by selectively demolishing DA neurons in the substantia nigra. Biologically, its metabolite 1-methyl-4-phenylpyridinium ion (MPP^+), produced *via* oxidation with monoamine oxidase (MAO)-B, persuades mitochondrial damage by impeding complex I during the mitochondrial electron transport chain, which as a result, impairs autophagic degradation and reduces mitochondrial DNA level (Zhu et al., 2012; Miyara et al., 2016). Studies affirmed that incubation of *C. elegans* with neurotoxin MPTP augments lethality and dwindles mobility, and the developments of these sturdy symptomatic flaws can be correlated to peculiar deterioration of the DA neurons (Braungart et al., 2004). Based on the following outcomes, several investigational studies utilized the MPTP-triggered *C. elegans* PD model to understand and screen new anti-PD drugs (Lu et al., 2010; Johnson et al., 2018; Lee et al., 2021). Lee et al. (2021) explored the neuroprotective effect of damaurone D in a *C. elegans* model of PD, and the results revealed significant alleviation in MPTP- induced neuronal damage and α-synuclein expression.

Likewise, MPTP, catecholaminergic neurotoxin 6-hydroxydopamine (6-OHDA) critically triggers PD-like pathology. Despite similar chemical structure to DA, the presence of hydroxyl group in 6-OHDA induces mitochondrial dysfunction, resulting in elevation of oxidative stress and ATP depletion, which consequently degrade DA neuronal activity (Glinka et al., 1997; Glinka et al., 1998; Blesa et al., 2012; Offenburger et al., 2018). Administration of 6-OHDA to *C. elegans* hamper DA cell bodies and their associated processes (Masoudi et al., 2014). Marvanova and Nichols (2007), screened the neuroprotective potential of several DA, NMDA, and GABA receptor agonists for 6-OHDA-induced DA neurotoxicity in *C. elegans,* and results showed that two D2 receptor agonists, quinpirole and bromocriptine, dose-dependently diminish 6-OHDA toxicity through receptor-independent mechanisms. TSP-17, tetraspanin family membrane proteins also restrain the DA transporter, DAT-1, in *C. elegans* and preserve DA neurons from 6-OHDA-induced neurotoxicity (Masoudi et al., 2014). Isoflorentin, an isoflavone from the roots of Belamcnda chinensis (L.) DC, significantly prevents DA neuronal deterioration and elevated life span in the 6-OHDA triggered PD model in *C. elegans*. Results also affirmed that isoflorentin also ameliorates α-synuclein accumulation in the *C. elegans* model, indicating it as a possible target agent for PD (Chen et al., 2015). Similarly, Betulin prevents neuronal damage and reverses lifespan dwindleness in the 6-OHDA-induced PD model in *C. elegans* with significant improvement in proteasomes activity with down-regulation of apoptotic pathways genes (Tsai et al., 2017). Furthermore, several other phytochemicals have been evaluated for their potent anti-PD activity using the 6-OHDA-induced PD model in *C. elegans* (Chalorak et al., 2018; Ma et al., 2020; Tsai et al., 2020; Chalorak et al., 2021; Li et al., 2021; Saewanee et al., 2021; Long et al., 2022; Muhammad et al., 2022).

Apart from neurotoxins, several insecticides and herbicides have also been employed to induce PD-like symptoms in *C. elegans* (Settivari et al., 2009; VanDuyn et al., 2010; Jadiya et al., 2013; Jadiya and Nazir, 2013; Jafri Ali and Sharda Rajini, 2013; Settivari et al., 2013). Studies confirmed that rotenone, a broad-spectrum insecticide, develops PD-like pathogenesis in NL5901 *C. elegans* by significantly elevating oxidative stress and α-synuclein aggregation. Moreover, the reduction in lipid content and mitochondrial activity in the worms indicate it as an environmental neurotoxin that triggers PD in *C. elegans* (Jadiya et al., 2013; Jadiya and Nazir, 2013; Zhou et al., 2013; González-Hunt et al., 2014). Similarly, monocrotophos, an Organophosphorus insecticide, declines DA neuronal integrity in both N2 and BZ555 type *C. elegans*, along with a significant reduction in locomotor rate and life span, when compared with MPTP (Jafri Ali and Sharda Rajini, 2013). Paraquat herbicides also elicit DA neurodegeneration in *C. elegans* by depleting mitochondrial DNA (González-Hunt et al., 2014). Marsova et al., 2020 demonstrated that *lactobacillus* fermentum U-21 protects *C elegans* from paraquat-induced oxidative stress and neurodegeneration (Marsova et al., 2020). Manganism, a neurological condition caused by overexposure to manganese,

provokes oxidative stress, irregular DA signaling, and cellular death and significantly induces PD-like symptoms in *C. elegans*. Administration of a high level of manganese to *C. elegans* can also be used as a toxin-induced *C. elegans* model of PD (Settivari et al., 2009; Settivari et al., 2013).

In Parkinson disease it has been difficult to deliver drugs to the brain in effective and well controlled manner. Nanotechnology's development has opened up new possibilities for the treatment of PD. A study by de Guzman et al. (2022), evaluated the impact of functional food nanocomplexes on PD prevention using a *C elegans* model system. The developed curcumin-loaded human serum albumin nanoparticles improve the body movement, basal slowing response, and dopaminergic neuron degeneration in the *C. elegans* model of PD, thus affirming the importance of nanomedicine in suppressing the emergence of symptoms of PD (de Guzman et al., 2022).

C. elegans models for amyotrophic lateral sclerosis

ALS is a genetically diverse ND Identify by the loss of motor neurons (brain and spinal cord), ultimately imparting ongoing paralysis of the body (Turner et al., 2013; Vériène et al., 2015). Neuroinflammation, mitochondrial dysfunction, and impairment in axonal transports are featured as cellular and molecular pathogenesis of ALS (Ferraiuolo et al., 2011; Rojas et al., 2020). Likewise PD, the etiology of ALS is familial and sporadic in nature, which involves numerous genes and proteins, including *fused in sarcoma (FUS,) transactive response DNA Binding Protein 43 (TDP-43)*, and *superoxide dismutase-1* (*SOD-1*) (Alexander et al., 2014; Vériène et al., 2015). ALS rodent models exhibit significant ALS pathology, but difficulty in manipulating several genes of ALS at once turned of *C. elegans* genes researchers to use simple organisms like *C. elegans* to model ALS toxicity (Therrien and Parker, 2014). Since 80% have human homologs, both Cholinergic and GABAergic neurons play a significant part in the locomotor activity of *C. elegans* (Jorgensen, 2005), thus making it a suitable model for the exploration of ALS and its pathogenesis.

Genetic *C. elegans* models

Mutation in the *SOD1* gene alters the enzyme's folding and stability, causing aggregation in motor neurons following paralysis (Wang et al., 2009; Caldwell et al., 2020). There are more than 160 mutations in the *SOD1* gene since 1993 (Al-Chalabi et al., 2012), making it the most common mutation in familial ALS, and the human SOD1 gene has a similar function to that of the *C elegans* gene. (Wroe et al., 2008; Turner et al., 2013). To date, numerous transgenic lines *C. elegans* models having mutant human *SOD1* gene have been effectively produced with motor neuron degeneration and paralysis characteristics like that of ALS patients (Oeda et al., 2001; Gidalevitz et al., 2009; Wang et al., 2009; Li et al., 2013; Thompson et al., 2014; Baskoylu et al., 2018; Osborne et al., 2021). Both G85R and G93R mutations in the *SOD1* transgenic worm exhibited severe Endoplasmic Reticulum (ER)-stress (Wang et al., 2009; Li et al., 2013). Interestingly, Baskoylu et al. (2018) generated a single-copy *SOD1* knock-in *C. elegans* strain with two mutations, G85R and G93R, using a novel CRISPR/Cas9-mediated genome editing technique. Li et al. (2013) developed a novel transgenic G93A mutant SOD1 *C. elegans* model to underline the role of autophagy in ALS. A4V mutation has also been discovered to induce ER stress, yet the mechanism remains unclear (Perri et al., 2020). Recently, Xu et al., (2022) affirmed the therapeutic potential of metformin in treating ALS by improving autophagy and lengthening lifespan *via* the daf-16 pathway, using *SOD-1* mutant transgenic *C. elegans*.

Mutation in *TDP-43* stimulates protein aggregation along with cytoplasmic mislocalization, which induces impaired motility (Liu et al., 2017). *TDP-43* orthologue tdp-1 presents in *C. elegans* postulate a promising relationship between genetic mutation and cellular pathology (Wegorzewska and Baloh, 2011). Firstly, Ash et al. (2010) developed the first *TDP-43* mutated transgenic *C. elegans* model for ALS, and the over-expression of *TDP-1* in worms induces GABAergic motor neuronal degradation with uncoordinated movement. Afterward, various *TDP-43* mutated strains have been developed, including *TDP-43A315T,* being widely used in understanding the pathogenesis of ALS (Vaccaro et al., 2012a; Zhang et al., 2012; Liachko et al., 2013). Noteworthy, Tauffenberger et al. (2013) explored the protective effects of several compounds, i.e., resveratrol, reserpine, trolox, propyl gallate, rolipram, and ethosuximide (earlier affirmed to boost longevity in *C. elegans*) against mutant *TDP-43* toxicity in motor neurons using transgenic TDP-43 models.

Likewise *TDP-43*, the mutation in the DNA/RNA-binding proteins, *FUS,* also aggregates protein to induce mortality impairment, and its overexpression alters synaptic functions (Ling et al., 2019). Several transgenic *C. elegans* models with mutated and overexpressed FUS gene has been developed (Vaccaro et al., 2012b; Murakami et al., 2012; Vériène et al., 2015; Ma et al., 2018; Markert et al., 2020; Labarre et al., 2021; Baskoylu et al., 2022). R524S and P525L mutated *FUS* transgenic ALS models for *C. elegans* have been created with impaired neuromuscular function and locomotion (Baskoylu et al., 2022). With the advancement in genetic manipulation, Labarre et al. (2021) recently developed a single copy *FUS* mutant transgenic strain of *C. elegans*, exhibiting similar ALS phenotypes, including GABAergic neurodegeneration with progressive paralysis. Knockdown *dnc-1/dynactin 1* ameliorates autophagosome transportation and stimulates motor neuron degeneration. Based on this, Ikenaka and their team developed a novel *dnc-1* knockdown transgenic model of *C. elegans* and furthermore employed this behavior-based model to identify and

evaluate drugs having a potential neuroprotective effect against motor neuron disease (Ikenaka et al., 2013; Ikenaka et al., 2019).

An extension of the hexanucleotide GGGGCC replication in the first intron of the C9ORF72 gene was recently linked to ALS; however, its mechanism is still unclear. The use of *C. elegans* can be a suitable approach to underline their association with ALS because of the presence of C9ORF72 homolog as alfa-1 (ALS/FTD associated gene homolog) (Therrien et al., 2013; Therrien and Parker, 2014; Rudich et al., 2017). Therrien et al., 2013 firstly developed a transgenic model that induces motor deficits in *C. elegans* by a mutation in *alfa-1*. homologe. Furthermore, it was also observed that the model demonstrated a synergistic toxic effect with *TDP-43* mutation (Therrien et al., 2013).

Toxin-induced models

Overexposure to metalloid selenium in the body has been concerned as an etiological factor of ALS (Vinceti et al., 2009; Kamel et al., 2012; Malek et al., 2012). Based on this, Estevez et al. (2012) developed a toxin-induced ALS model in *C. elegans* using sodium selenite as a neurotoxin. Exposure to a high dose of sodium selenite triggers neurodegeneration of cholinergic neurons, followed by paralysis (Estevez et al., 2014). Furthermore, it was also observed that a decrease in insulin/insulin-like (IIS) signaling by elevating *PTEN* and *PINK1* gene expression overcomes selenium-induced motor defects (Estevez et al., 2014).

C. elegans models for Huntington's disease

HD is an incurable, autosomal-dominant adult-onset ND characterized by a reduction in motor and memory functions (Orr and Zoghbi, 2007; Dayalu and AlbinHuntington, 2015). Polyglutamine (polyQ) stretch and expansion in the N terminus of Huntington protein (HTT), by an atypical CAG triplet, replicated extended mutant in Huntington gene, is the prime cause for its induction, with oxidative stress, irregular neuronal metabolism, and cytoplasmic inclusions as major pathological manifestations (MacDonald et al., 1993; DiFiglia et al., 1997). The developed polyQ expansions promote aggregation and misfolding of HTT, which subsequently alters the neurotransmitter uptake and release (Poirier et al., 2005). Despite several mammalian models available, *C. elegans* may endow better polyQ-induced toxic outcomes and help explore new therapeutic targets for HD.

Genetic *C. elegans* models

Although HTT ortholog is absent in *C. elegans*, numerous polyQ tract and human HTT fragments expressing transgenic *C. elegans* models have been designed in different neuronal subtypes to investigate the pathogenesis of HD (Faber et al., 1999; Satyal et al., 2000; Parker et al., 2001; Morley et al., 2002; Nollen et al., 2004; Parker et al., 2004; Poirier et al., 2005; Lee et al., 2017). Faber et al. (1999), developed the first transgenic HD model in *C. elegans*, having 150 repeat polyQ replicates (HTT-Q150) and inducing sensory neuron degradation. Later on, it was also observed that loss of polyQ enhancer-1 gene (*pqe-1*) further worsens the neurodegeneration; however, its overexpression attenuates Htt-Q150- induced neurotoxicity (Faber et al., 2002). Using these transgenic models, several phytochemical and chemical moieties have been evaluated to be developed as a potential therapy for the treatment of HD (Voisine et al., 2007; Tauffenberger et al., 2012; Boasquívis et al., 2018; Landon et al., 2020; Cordeiro et al., 2021). Glucose exhibited DAF-16 dependent neuroprotective effect in the 128-repeat polyQ HD model (Tauffenberger et al., 2012). Recently, Corerio et al. (2021), demonstrated the neuroprotective potential of rutin against polyQ-induced neurodegeneration using various transgenic *C. elegans* strains, i.e., Bristol N2 (wild-type), AM141, AM101 (Q40 over-expressed), HA759 (H150 over-expressed), CL 2070, and CF1553, and results showed a significant reduction in polyQ-induced neuronal death with DAF-16 up-regulation (Cordeiro et al., 2021). A study using primary cell culture neurons and *C. elegans* polyQ poisoning model also showed that acetylation of mutant *Htt* at *K444* enhanced mutant Htt clearance and neuroprotection (Jeong et al., 2009).

The size of the CAG repeats also affects the aggregation phenotype in *C. elegans*, just as it does in humans. At least three models have been developed to produce polyglutamine-associated neurotoxicity in neurons by enlarging polyglutamine sequences in sensory neurons, touch receptor neurons, or the whole nervous system of C worms (Faber et al., 1999; Parker et al., 2001; Brignull et al., 2006). The body wall muscle cells of the worm *C. elegans* have been used like in A.D. to imitate polyglutamine aggregation (Morley et al., 2002).

Implication of nanotechnology and nanomedicine can be a possible intervention to treat HD by preventing aggregation of Huntington protein. Selenium nanoparticles developed by Cong et al. (2019) significantly diminishes neuronal death, restores behavioral dysfunction, and protected *C. elegans* neuronal damage by impeding oxidative stress, huntington protein aggregation, and down–regulation of histone deacetylase enzyme. The results affirmed that nanomedicine can be used as a effective approach to improve HD therapy.

Conclusion and future prospective

The widespread prevalence of NDs highlights the urgent need of ingenious approaches to identify novel therapeutic targets and disease-modifying elements. AD, PD, ALS, and HD have become more common in recent years. As models

of human nervous system, worms share structural and functional similarities. Also, visualizations of neurons and synapses in worms, correlation between neuronal activity and behavior in worms attract interest for development of experimental models with *C. elegans*. Genetic manipulations make it possible to recognize genes involved in neuronal formation, migration or other functions. Past half century, numerous significant discoveries have completely changed our understanding of biology using the nematode *C. elegans* as the experimental subject. The *C. elegans* is an excellent model for studying neurodegeneration and aging, and discovering numerous signaling pathways involved in longevity. There have also been innumerable models of neurodegenerative illnesses created using either worm genome mutations or the expression of human proteins linked to neurodegeneration (such as β-amyloid, α-synuclein, polyglutamine) in specific worm tissues.

The development of *C. elegans* models to investigate the genetic causes of NDs continues to open new doors for medical research and helped in identifying possible therapeutic targets for specific conditions. The *C. elegans* models discussed in this review demonstrate that malfunctioning and misfolded proteins cause harmful aggregation and impair critical cellular functions. Although *C. elegans* exhibits several advantageous characteristics for aging and neurodegenerative studies, yet there are several drawbacks with *C. elegans* as a model that should not be overlooked while considering its usefulness. Many distinct organs, including the liver, lungs, skin, and blood circulation system, are absent in this primitive organism. Nevertheless, they lack epinephrine, norepinephrine, histamine signaling, and several other notable differences in sodium-dependent channels. Researchers continue to use the benefits of utilizing *C. elegans* to study various aspects of neurodegeneration, from the genetic routes leading to neuronal death to how various disease-associated molecular pathways might cause neuronal damage. However, further investigation is required to determine which molecular processes cause and contribute in aging.

Increasing access to high-throughput chemical-genetic screenings and the possibility of assessing toxic mixture effects have led to the increased use of *C. elegans* in toxicological investigations. Because mammalian models have long life cycles, it is challenging to measure chronic and delayed effects of environmental toxins. Short lifespan of *C. elegans* is making it easy to measure these effects, yet still require more consideration in toxicological investigations.

Furthermore, due to the restricted ability of therapeutic molecules to penetrate the blood-brain barrier, the treatment of neurodegenerative illness continues to pose a formidable challenge. Because of their unique physico-chemical characteristics and capacity to traverse the blood-brain barrier, nanoparticles offer multifunctional accommodations for resolving these biomedical and pharmacological problems. Numerous CNS-related illnesses like AD, PD, ALS and HD may benefit from integrating nanomedicine and neuroscience. The variety of nanoparticles now in the market needs to go through rigorous stability and toxicity testing. They must also be tailored for gene or medication delivery to the CNS. To better under the nanoformulation efficacy, *C. elegans* models are the novel and suitable approach. However, more studies should be done to describe improved tracking of the origin of NDs and nanoparticle mobility. In the near future, we earnestly anticipate an increase in the use of nanomedicine to treat neurodegenerative diseases.

Author contributions

PC: reviewing, writing. KW: reviewing, writing. GS: conceptualization, framing, reviewing, proof reading.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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