

Exploring The Role Of Selenium And Its Nanoformulation In The Progression Of Neurodegenerative Diseases: A Review

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Abstract

Selenium has been used traditionally for its various roles in traditional dosage forms, specifically for enhancing memory and overall human health. As per a recent research study, selenium is found to be safe. The positive role of selenium and its protein (SELENOP) promises to control and manage neurodegenerative diseases by directly and indirectly interacting with the pathophysiology of neurodegenerative diseases like Alzheimer's disease (AD), Parkinson's disease (PD), and Huntington's disease (HD). Selenium, combined with established drugs for neurodegenerative diseases, is explored in its nanoformulation, elevating its therapeutic action. Selenium can be a good candidate in exploring prevention and managing less explored diseases like Huntington's disease (HD) and other neurodegenerative diseases. Selenium is used as a neuroprotective agent by redox regulation and antioxidant defense mechanisms, which protect neurons from oxidative damage.

Keywords: Neurodegeneration, Selenium, Nanoformulation, Alzheimer's Disease, Parkinson's Disease, Huntington's Disease.

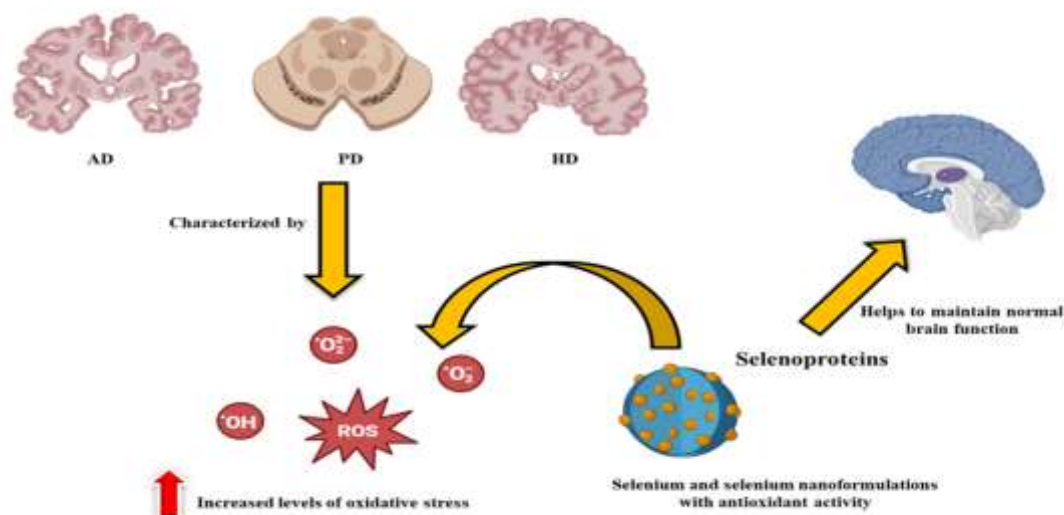


Fig: Graphical Abstract

List of Abbreviations:

AD- Alzheimer's disease	DPPH- 2,2-diphenyl-1-picrylhydrazyl
PD- Parkinson's disease	GSK-3β- Glycogen synthase kinase-3 beta
HD- Huntington's disease	STAT3-
WHO- World Health Organization	Signal Transducer and Activator of Transcription 3
Aβ- Amyloid- β	BBB- Blood-Brain Barrier
HTT- Huntingtin gene	HUVEC – Human umbilical vein endothelial cells
FDA- Food and Drug Administration	TGN- Trigeminal neuralgia
GP- Glutathione peroxidases	Tet-1- Tet Methylcytosine Dioxygenase 1

SeP / SELENOP - Selenoproteins UGA - Uracil, guanine, and uracil codon DIO - Deiodinases TrxR - Thioredoxin reductases GSH - Glutathione ROS - Reactive oxygen species EDL - Extensor digitorum longus FDB - Flexor digitorum brevis ApoE - Apolipoprotein E DNA - Deoxyribonucleic Acid EC50 - Half maximum effective concentration	Nrf-2 – Nuclear factor erythroid 2-related factor 2 SOD - Superoxide Dismutase CAT - Catalase MPP⁺ - 1-methyl-4-phenyl pyridinium POD - Peroxidase Poly Q - Polyglutamine PVP - Polyvinylpyrrolidone AchE - Acetylcholinesterase BuchE - Butyrylcholinesterase
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1. Introduction:

Overall, 416 million people globally had different stages of AD, with about 22% of patients aged above 50 years. Over 8.5 million people were diagnosed with PD in 2019. WHO estimated that PD caused about 329,000 deaths globally [1]. The pooled prevalence of HD was found to be 4.88 per 100,000, with a higher number of patients in Europe and North America [2]. Although neurodegeneration is at the core of these disorders, there are multifactorial pathways involved in the pathogenesis of these diseases. Such varied mechanisms of pathogenesis make it quite tricky to find therapeutic alternatives aimed at modifying the disease parameters. One of the crucial trace elements is selenium, which is responsible for maintaining good brain health [3]. Organic forms of selenium in the body include selenocysteine and selenoproteins. Different selenoproteins play various roles in the body through cell-to-cell signaling mechanisms [3]. A decrease in the level of selenium is one of the leading causes, which triggers several neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, and Huntington's disease [4]. Treatment of selenium has shown synergistic antioxidant activity in combination with therapeutic agents, such as nanoformulation of selenium, and its combination was found to be more effective and possesses a broad future scope [5]. This review will try to focus on the role of selenium in the progression of various neurodegenerative diseases like Alzheimer's disease (AD), Parkinson's disease (PD), and Huntington's disease (HD). The underlying mechanisms of the diseases and the role of selenium in controlling them are explained in the present review. This review aims to establish the correlation between selenium treatments and their various nanoformulation in controlling and managing the aforementioned neurological disorders.

1.1 Neurodegenerative Disorders Mechanism:

Neurodegeneration is one of the crucial mechanisms associated with various brain diseases. Neurons are involved in cell-to-cell signaling. Neurodegeneration can lead to neuronal dysfunction, hampered neural networks, cytoskeletal abnormalities, altered homeostasis, neuroinflammation, and neuronal cell death [6] [7]. A primary characteristic of all neurodegenerative diseases is the formation and accumulation of complex protein aggregates [8]. Based on the altered proteins, neurodegenerative diseases can be categorized as follows (Fig 1).

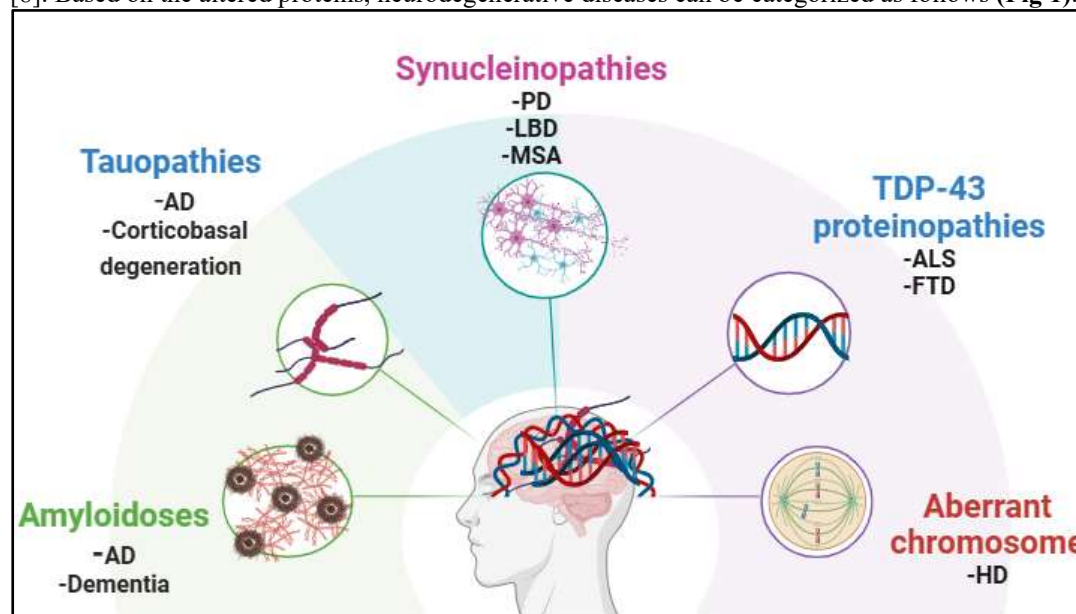


Fig 1: Neurodegenerative diseases based on their causative protein.

Alzheimer's disease is characterized by the formation of extracellular aggregates of A β and intracellular

neurofibrillary tangles composed of tau protein. A result of this is gliosis, loss of synapses, neuronal damage, and death [9] [10] [11]. There is also a loss of cholinergic neurons and a significant decrease in the levels of acetylcholine, which hampers the cognitive and learning functions of the brain [12, 13]. The formation of amyloidosis is one of the major causes that leads to Alzheimer's. These proteins are found in the cytoplasm of neurons and glial cells. Extracellular deposition of these proteins results in the formation of amyloid plaques, which are noted to have various morphological forms and include diffuse, dense-colored, classical, and cotton wool plaques. The most common product of this protein is the amyloid- β ($A\beta$) formed upon degradation of amyloid-precursor protein (APP). Such $A\beta$ malformed deposits have been found in various diseases, including Alzheimer's disease (AD), Creutzfeldt-Jakob disease (CJD), familial British dementia, and familial Danish dementia.

Intracellular aggregates of misfolded α -synuclein characterize Parkinson's disease in the spinal cord and sympathetic ganglia. Furthermore, there is a significant loss of dopaminergic neurons present in substantia nigra pars compacta, disruption of mitochondrial function, oxidative stress, and neuroinflammation [14] [15]. Aggregation and accumulation of presynaptic protein α -synuclein present within the neurons and glia. Disorders like Parkinson's disease (PD), Lewy-body dementia (LBD), and multiple system atrophy (MSA) (Fig 1).[16] A mutation caused in the HTT gene by repeat fragments of the amino acid glutamine is the root cause of HD. Neuroinflammation, microglial activation, mitochondrial dysfunction, striatal degeneration, and neuronal death are hallmarks of this disease [17].

The current treatment strategy involves the use of a drug that gives symptomatic relief from Neurological disorders. The current therapeutic option available for the treatment of neurodegenerative diseases. For Alzheimer's, cholinesterase inhibitors like donepezil, rivastigmine, and galantamine, N- N-methyl D-aspartate (NMDA) antagonist memantine, and recently approved anti-amyloid drugs lecanemab and aducanumab [18] and for Parkinson's, several classes of drugs like dopamine precursors including levodopa, carbidopa, or a combination of them, catechol-o-methyl transferase inhibitors like entacapone, tolcapone, and opicapone, dopamine agonists like pramipexole, ropinirole, apomorphine, rotigotine, monoamine oxidase B inhibitors like rasagiline, selegiline, safinamide. NMDA antagonists, such as amantadine and adenosine 2A antagonists, like istradefylline, as well as anticholinergics like trihexyphenidyl and benztropine, are employed. Only two drugs, tetrabenazine and deutetabenazine, have been approved by the FDA against HD [19]. There is a limited number of options for therapy, and there is a subsequent need to find newer alternatives as supplementing the current treatment or as a novel therapy option all by itself.

2. Selenium in Brain Health:

Selenium is an essential trace element. The organic forms of selenium in the body include selenocysteine and selenoproteins [20, 21]. A total of 25 different selenoproteins exist in the body with varied roles in diverse body mechanisms (Table 1). They are subdivided into three categories: glutathione peroxidases (GPx), thioredoxin reductases, and deiodinases. Glutathione peroxidases GPx1, GPx2, GPx3, GPx4, GPx6, SelP, SelK, and SelM are involved in antioxidant defense mechanisms (Fig. 2). Selenoproteins are synthesized through a complex mechanism involving the selenocysteine incorporation into the polypeptide chain, often facilitated by specific codons (UGA) and unique translation machinery. Regulation of selenoprotein expression is influenced by selenium availability, dietary intake, and cellular redox state. Many selenoproteins, including glutathione peroxidases and thioredoxin reductases, are essential for detoxifying reactive oxygen species (ROS) and protecting cells from oxidative damage [22]. Selenoproteins are involved in the synthesis and metabolism of thyroid hormones, crucial for metabolic regulation and development [23]. Some selenoproteins modulate immune responses, influencing inflammation and the body's defense mechanisms. The altered expression of selenoproteins has been linked to various cancers. Some selenoproteins exhibit tumor-suppressive properties, while others may promote cancer cell survival [24] Selenoproteins contribute to cardiovascular health by regulating inflammation and oxidative stress. Deficiencies are associated with an increased risk of heart disease. In conditions like Alzheimer's and Parkinson's disease, selenoproteins may protect against neurotoxicity and oxidative damage. Dysregulation can exacerbate disease progression. Selenoproteins play a role in glucose metabolism and insulin signaling [25]. Imbalances may contribute to conditions such as diabetes and obesity. Factors such as thyroid hormones and specific transcription factors also play a role [22].

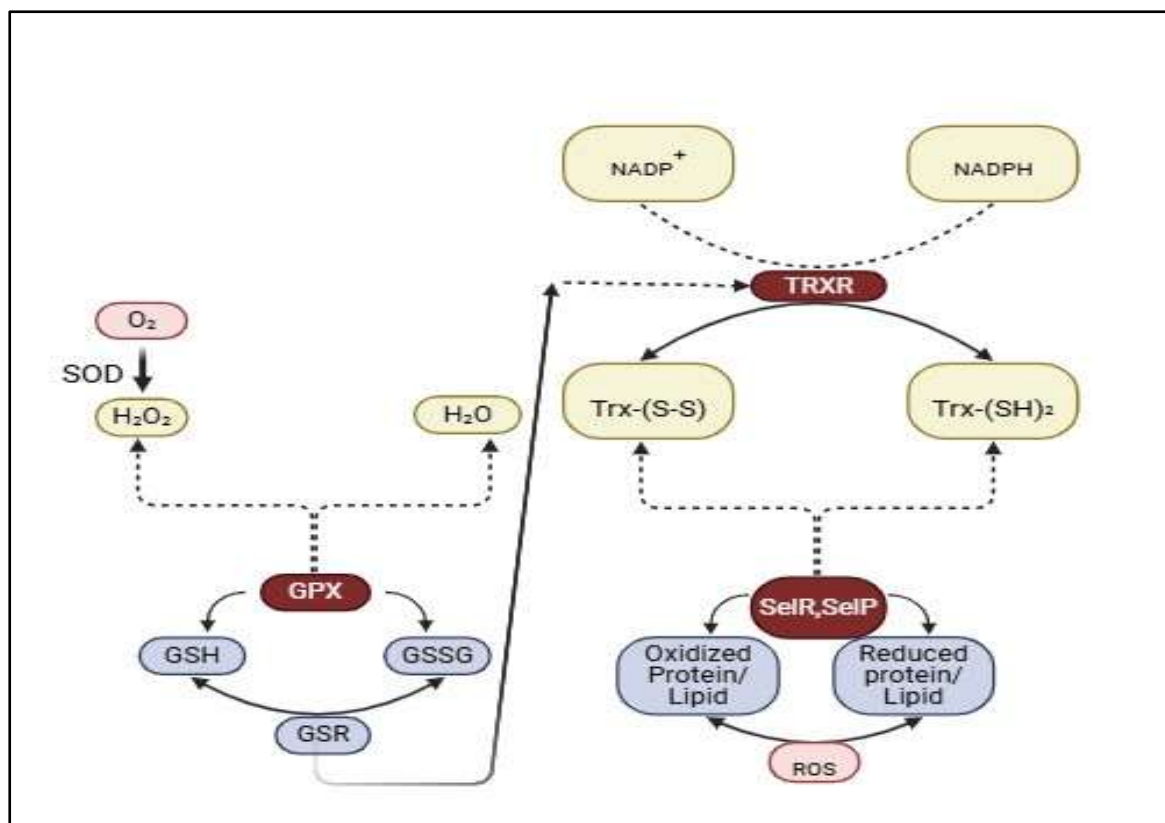
The brain is known to retain selenium the most among all the organs[26]. A positive correlation was observed with cognition corresponding to the selenium level [27]. Irreversible damage has been closely associated with selenium deficiency. Selenoproteins play a significant role in antioxidative mechanisms with the help of particularly glutathione peroxidases (GPXs) and thioredoxin reductases (TrxRs), which protect neurons from oxidative stress by detoxifying reactive oxygen species (ROS) [3]. By reducing oxidative damage, they help maintain neuronal integrity and function. Selenium influences the synthesis and metabolism of neurotransmitters, including dopamine and serotonin, which are crucial for mood regulation and cognitive function; as a result, they play a role in the regulation of neurotransmission. Selenoproteins can help regulate inflammatory responses in the brain, potentially reducing the risk of neuroinflammatory conditions as this selenoprotein also acts like a

neuroinflammation modulator. Selenoproteins contribute to neuronal survival by preventing apoptosis and promoting cellular resilience against stressors [28] SelM and SelN aid with protein folding. (SELENOP) SelP has a role in metal detoxification. GPx4 is a component of sperm structural protein, SelI in phospholipid synthesis, SelN in calcium signaling, SelH as a transcription factor, SelR in the reduction of oxidized methionine groups, SelS in the removal of misfolded proteins, SelT in calcium mobilization, SelW in synaptic localization, iodothyronine deiodinases DIO1,2, and 3 in thyroid metabolism are some key functions of selenoproteins. Thioredoxin reductases TrxR1, TrxR2, TrxR3, SelH, and SelO carry out redox signaling. (Fig 2) SelV has been identified, but its function is not yet discovered [28] [29]

Table 1. Selenoproteins and their functions

Selenoproteins	Selenoproteins Functions	Reference
SelF	Essential for biological functions	[30]
SelM & SelN	Protein folding and supports cellular growth.	[20]
SelP (SELENOP)	Metal detoxification	[20, 21]
SelI	Phospholipid synthesis	[31]
SelN	Calcium signaling	[31]
SelH	Transcription factor	[28]
SelR	Reduction of the oxidized methionine group	[32]
SelS	Removal of misfolded proteins	[28]
SelT	Calcium Mobilization	[28]
SelV	Function not discovered	[28, 29, 31]
SelP, SelK, SelR, and SelM	Antioxidant defense mechanism	[20]
Thioredoxin reductase (TrxR1-3, SelH and SelO)	Redox signaling	[28]
Glutathione peroxidases (GPx1-6)	Antioxidant defense mechanism	[20]

Selenoproteins directly reduce Reactive Oxygen Species (ROS) by reducing ROS and preventing cellular damage. For instance, GPXs convert harmful peroxides into less reactive species. Selenoproteins assist in regenerating other antioxidants, like glutathione, through their enzymatic activities. This regeneration is crucial for maintaining a high antioxidant capacity within cells. Selenoproteins can influence redox signaling pathways, impacting cellular processes such as apoptosis, inflammation, and stress responses. By regulating the balance between oxidation and reduction, they help maintain cellular health. Glutathione Peroxidases (GPXs) function by reducing hydrogen peroxide (H₂O₂) and lipid peroxides to water and alcohols, respectively, using glutathione (GSH) as a substrate. Selenium in the form of selenocysteine is integral to the active site of GPXs, allowing these enzymes to catalyze the reduction of peroxides efficiently [3]. Thioredoxin Reductases (TrxRs) function by maintaining the redox state of thioredoxin, a small protein that reduces other proteins by thiol-disulfide exchange, thus aiding in the repair of oxidative damage [23]. TrxRs utilize NADPH to reduce oxidized thioredoxin, with selenocysteine playing a vital role in the enzyme's catalytic function. Selenoprotein P (SelP) functions by involving in selenium transport and has antioxidant properties [24]. It protects cells from oxidative damage by reducing ROS levels and can transport selenium to various tissues, enhancing overall antioxidant capacity. Selenoprotein K (SelK) functions by implicating in protecting cells against oxidative stress and modulating immune responses. It helps maintain ER function and prevents apoptosis induced by oxidative stress.



a) GSH-dependent antioxidant system b) TRX-dependent antioxidant system

Fig 2: Overview of selenoproteins in cellular antioxidant

GPX, TRXR, SEIR, and SEIP are selenoproteins that play a significant role in the cellular antioxidant system by participating in GSH- and TRX-dependent antioxidant mechanisms.

a) GPXs catalyze the breakdown of peroxides in water in the presence of GSR (glutathione reductase) and SOD (Superoxide dismutase).

b) TRXRs reduce oxidized TRXs, where TRX are used as a source of electron donors for detoxification of oxidized proteins and lipids such as protein phosphate, protein kinase, and membrane protein by formation of redox complex.

Selenium is stated to have a calcium ion influx effect [33]. A positive correlation has been observed between selenium treatment and voluntary muscle performance in mice. Animals receiving the higher concentration of 5 ppm selenite and nano selenium showed significant improvement in voluntary muscle performance compared to the control[34]. The processes in EC (excitation-contraction) coupling were thoroughly examined to elucidate the underlying mechanics. Shortly after two weeks of using selenium alone, they observed comparable benefits in mice's in vitro performance on the force in EDL (extensor digitorum longus) and SOL (in vitro force in soleus). Since the flexor digitorum brevis (FDB) and EDL muscles contain essentially exclusively fast-twitch fibers, the results of isolated muscle fiber tests on FDB and whole muscle experiments on EDL and SOL are reconcilable. There is a strong correlation between the increased force development in the EDL of the same animal and the greater intracellular $[Ca^{+2}]$ change during depolarisation in the FDB fibers of Se-supplemented mice.

The human study's focus on patients with facioscapulohumeral muscular dystrophy highlights the potential use of selenium in medicine. They concluded that mice's muscle function benefits from selenium, and NanoSe absorbs its effects at low concentrations. It raises the expression of selenoprotein N in the muscles and the amount of releasable calcium in the intracellular reserves. According to their findings, a low-dose selenium supplement combined with an antioxidant strategy may be a helpful treatment method for myopathy patients. It may also help prevent sarcopenia in the elderly. Selenium deficiency is also associated with compromised motor function, such as Alzheimer's, Parkinson's, and Huntington's diseases [31]. Selenium also has several other functions, such as antioxidants, modulation of neurogenesis, and maintenance of mitochondrial dynamics. It was thus observed that selenium and selenoproteins are involved in varied bodily functions, and alterations of this metal could cause significant changes in the normal body functions, typically of the brain. Selenoprotein F (SelF) is a member of the selenoproteins family, distinguished by its incorporation of selenium, which is essential for various biological functions. SelFs play a role in protein folding and secretion and are significant in cellular process triggers. Misfolded proteins also lead to different neurodegenerative diseases [30]. SelF is involved in the proper folding

of newly synthesized proteins in the endoplasmic reticulum (ER). It assists in the formation of disulfide bonds, which are crucial for the structural stability of many proteins. By facilitating the correct folding of proteins, SelP plays a critical role in the secretory pathway. Misfolded proteins can lead to cellular stress and diseases, making SelP's function vital for maintaining protein homeostasis. Imbalance in SelP triggers neurodegenerative disorders, metabolic disorders, and cancer. Dysregulation of SelP may contribute to conditions such as Alzheimer's and Parkinson's diseases, where protein misfolding and aggregation are prominent features. SelP's involvement in protein processing suggests a link to metabolic syndromes. Altered expression or function could affect insulin signaling and other metabolic pathways. Changes in the expression of SelPs have been observed in various cancers, indicating a potential role in tumor progression and response to therapy.

Altered selenium levels and selenoprotein expression have been linked to Alzheimer's disease. Selenium's antioxidant properties may help protect against the oxidative stress associated with amyloid-beta plaques [35]. In Parkinson's disease, selenoproteins may influence the aggregation of alpha-synuclein, a key pathological feature [27]. Adequate selenium levels help reduce oxidative stress and improve mitochondrial function, which are important in neuroprotection. Selenium deficiency has been associated with increased oxidative stress and inflammatory responses in multiple sclerosis. Selenoproteins may play a role in mitigating these effects and supporting neuronal health. Research suggests a link between selenium deficiency and mood disorders, including depression and schizophrenia [36]. Selenoproteins may influence neurotransmitter systems and neuroinflammatory pathways that are implicated in these conditions. Low selenium levels have been correlated with cognitive decline and increased risk of neurodegenerative diseases in older adults, emphasizing the importance of selenium in brain health [22].

2.1 Selenium in Neurodegenerative Disorders: Experimental Evidence:

The decline of selenium is age-related and has a direct link with age-related neurodegenerative disorders [37] [38]. A recent study using knockout mouse models confirmed that SEPP1 (Selenoprotein P) and its receptor low-density lipoprotein receptor-related protein 8 (LRP8) are required for the exercise-induced increase in adult hippocampal neurogenesis [39]. Selenium supplementation (between 0.05 -0.1 μM) not only increases neurosphere generation isolated from the subventricular zone but also significantly increases the neurosphere number and its size ($>150 \mu\text{m}$ in diameter). Further selenium supplementation in the form of sodium selenite or seleno-L-methylcysteine was found to increase the number of viable cells in adherent hippocampal precursor cells; this suggests that selenium does not alter the percentage of apoptotic neural precursor cells-NPCs (annexin V⁺). A dose-dependent increase in $\beta\text{III-tubulin}^+$ neurons from DG-derived neurospheres and selenium supplementation was also observed in both ex-vivo and in-vivo experiments. This study suggests a significant positive correlation between selenium supplementation and increased NPC proliferation and neuronal lineage differentiation potential without altering apoptotic cell death. The study also confirms that an exercise-induced increase in antioxidant selenium levels activated quiescent hippocampal NPCs, which results in NPC proliferation and neurogenesis. Mimicking the exercise-induced increase in systemic selenium transport by dietary supplementation was found to restore neurogenesis and reverse cognitive decline associated with aging and hippocampal injury [39] [40]. In Alzheimer's disease, a significantly lower plasma selenium level was found to be associated with AD patients compared to normal individuals [41].

In AD, selenoprotein P (SELENOP) (SelP) has been stated to possess a key role in the pathogenesis of AD. It is composed of 10 residues of selenocysteine and is the main transport protein of selenium in the body. Oxidative stress is one of the key mechanisms for the pathogenesis of AD, and thereby, selenoproteins bearing a natural antioxidant activity were suggested to have a potential role in preventing AD development.

The transport of selenium into the brain is carried out by binding (SELENOP) SelP to the ApoE receptor (**Fig 3 a**). Mutations of this ApoE receptor, which are known to be involved in AD pathology, can lead to low uptake of selenium. (SELENOP) SelP can bind toxic metals like copper, zinc, and iron, which are known to bind to A β . There is a possibility of a ternary complex of metal ions and A β with (SELENOP) SelP, which could potentially be less toxic than A β plaques (**Fig 3 b**). [42] [43]. Selenium in the form of selenite was found to reduce A β 40, A β 42, and γ - secretase activity and also protect against A β toxicity in cortical neurons in vitro. SelS has been implicated to play a role in preventing neurofibrillary tangles. Selenium deficiency increases the translocation of nuclear factor κB (NF- κB), which triggers the release of proinflammatory cytokines [42]. (SELENOP) SelP also conferred protection from oxidative stress to the astrocytes in vitro. Misfolded proteins in the endoplasmic reticulum need to be corrected by the endoplasmic reticulum-associated degradation (ERAD) system.

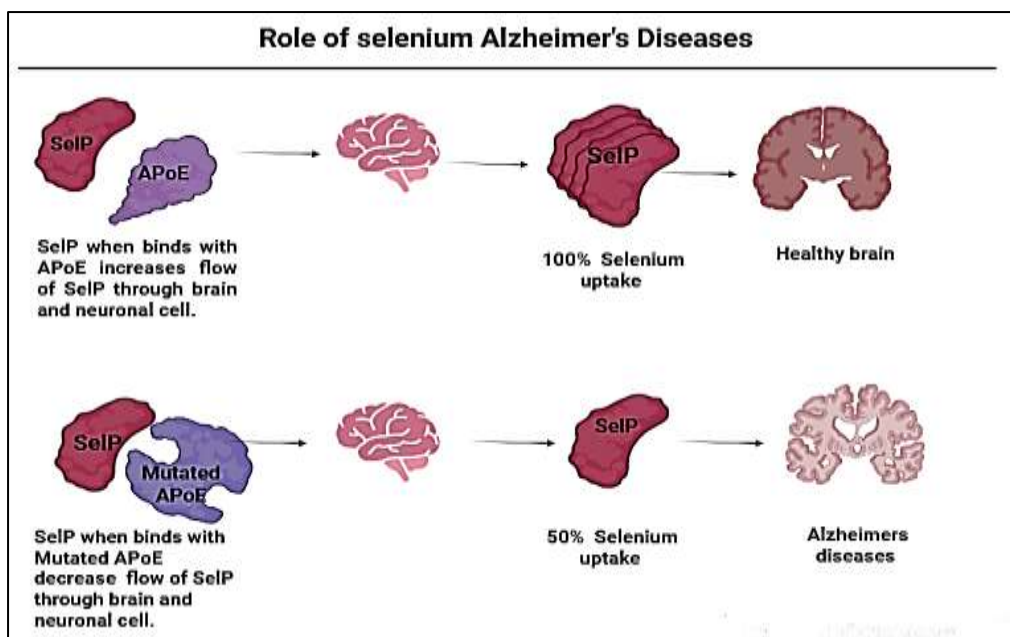


Fig 3.a

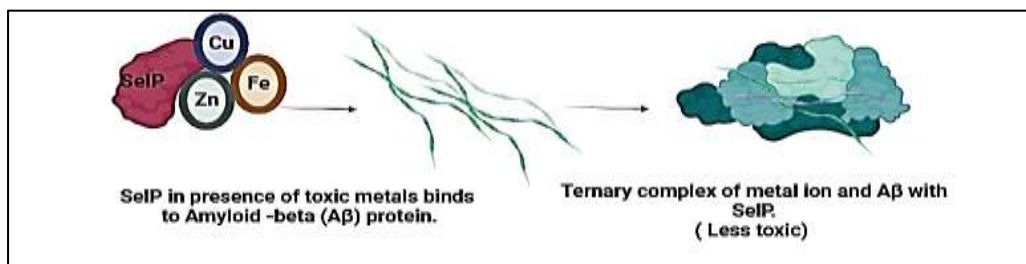


Fig 3.b

Fig 3. Role of Selenoproteins SelP in Alzheimer's Disease

SelS has a role in the normal function of the ERAD system and can thus possess preventive ability against the formation of neurofibrillary tangles [44]. When misfolded proteins accumulate, the ER activates the UPR, a cellular stress response aimed at restoring normal function. UPR pathways enhance the expression of chaperones and reduce the load of new proteins entering the ER, thereby promoting the degradation of misfolded proteins through ER-associated degradation (ERAD). (SELENOP) SelP-deficient mice showed deficient learning and deficient long-term potentiation compared to controls. SelR is essential to maintain redox balance, thereby preventing Aβ aggregation [45]. AD is also associated with endoplasmic reticulum-related stress caused by the presence of Aβ [31].

In Parkinson's disease, selenium is a component of several antioxidant enzymes, such as glutathione peroxidase. A deficiency can lead to increased oxidative stress, which can damage neurons and contribute to neurodegeneration. Selenium has anti-inflammatory properties. Low levels can result in increased inflammation in the brain, which is associated with the progression of Parkinson's disease. Selenium is important for proper thyroid function, and thyroid hormones are essential for brain health. Deficiency may lead to thyroid dysfunction, potentially affecting neurological health. Selenium influences the metabolism of neurotransmitters, such as dopamine. Low selenium levels might disrupt dopamine synthesis or regulation, which is critical in Parkinson's disease. Selenium was shown to protect against bradykinesia associated with PD. It also protected against DNA damage in lymphocytes in rat models. It was also revealed to partially protect against dopamine depletion. A positive correlation of selenium is stated with walking speed in older women equal to or above 65 years of age. In rat models, protection against locomotion was conferred upon the administration of sodium selenate. Degeneration of dopaminergic neurons is conferred by reduced activity of glutathione peroxidases [44, 45].

SelS lessens neuroinflammation by lowering levels of proinflammatory cytokines. Specific selenoproteins, such as glutathione peroxidases, help mitigate oxidative damage in the brain. Their expression levels can influence neuronal health and come back against precursors associated with PD [46]. Alpha-synuclein accumulation is a protein that aggregates into Lewy bodies, a hallmark of Parkinson's disease. Its misfolding and accumulation are central to the disease's pathology. There is emerging evidence suggesting that oxidative stress may promote the misfolding of alpha-synuclein, potentially linking selenium's protective role to its impact on this protein. Some

studies indicate that alterations in selenoprotein expression may influence alpha-synuclein aggregation and toxicity. For instance, insufficient selenium levels could exacerbate oxidative stress and promote alpha-synuclein-related pathology. Adequate selenium and selenoprotein levels might help prevent or mitigate alpha-synuclein aggregation through enhanced antioxidant defense mechanisms.

In another cross-sectional study establishing the link between Se, selenoproteins, and PD, it was observed that increased serum Se level and (SELENOP) SelP levels could be a biomarker or risk factor associated with PD. SelP transports to the brain and neural cells and induces more SelS which prevent the aggregation of misfolded protein [46]. Plasma selenium levels were found to be decreased in PD patients (Fig 4). [31]. Higher blood selenium levels were also correlated to neuroprotection in PD patients [47]. A deficiency of selenium was associated with an enhanced risk of oxidative stress caused by dopaminergic neurons. Selenium deficiency was found to be responsible for neurodegeneration and had the potential to cause PD. Selenium is crucial for the production of antioxidant enzymes like glutathione peroxidase.

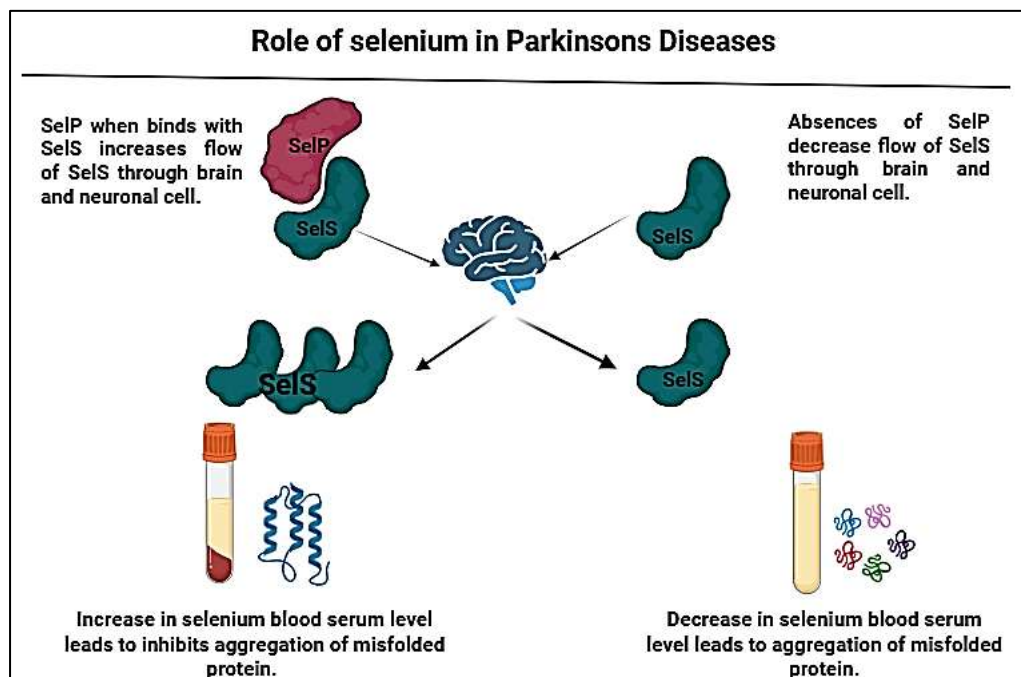


Fig 4: Role of Selenium in Parkinson's diseases.

Deficiency can lead to increased oxidative stress, which may exacerbate neuronal damage and contribute to the progression of HD. Selenium has anti-inflammatory properties. Low selenium levels may result in heightened neuroinflammation, which can worsen neurodegeneration associated with Huntington's disease. Selenium is important for mitochondrial health. Impaired mitochondrial function is observed in HD, and selenium deficiency could further compromise energy metabolism in neurons. Some studies suggest that selenium may influence gene expression related to neuroprotection. Deficiency could affect the expression of proteins involved in neuronal survival and function. The Gpx activity was significantly increased in HD patients to counteract oxidative stress, especially GPx1 and GPx6 [31]. Selenium was stated as an antioxidant therapy alternative in HD owing to its ability to improve neuronal morphology. Animal models showed a reduction in ipsilateral turning and significant improvement in behavior when treated with selenium compared to controls [48]. Diphenyl selenate was found to decrease neuronal death and levels of reactive oxygen species (ROS) in the *C. elegans* model of HD [49]. Selenium pretreatment in rat models that were induced with HD using quinoline displayed decreased quinoline-induced circling behavior, mitigated depleted γ -amino butyric acid (GABA) stores in the striatum, reduced neuronal damage, and prevented morphological alterations partially[50]. Indicating the beneficial effects of selenium in the treatment of Huntington's disease. Various nanoformulation approaches have been adapted to overcome AD, PD, and HD pathologies along with some already existing drugs or in the form of monotherapy (Table 2).

3. Selenium Formulation for Neurodegenerative Disorders:

Nanoformulation of selenium and its combined formulation (Fig 5) has future scope for neurodegenerative diseases such as Alzheimer's, Parkinson's and Huntington's, which occurred due to one of the reasons of selenium deficiency.

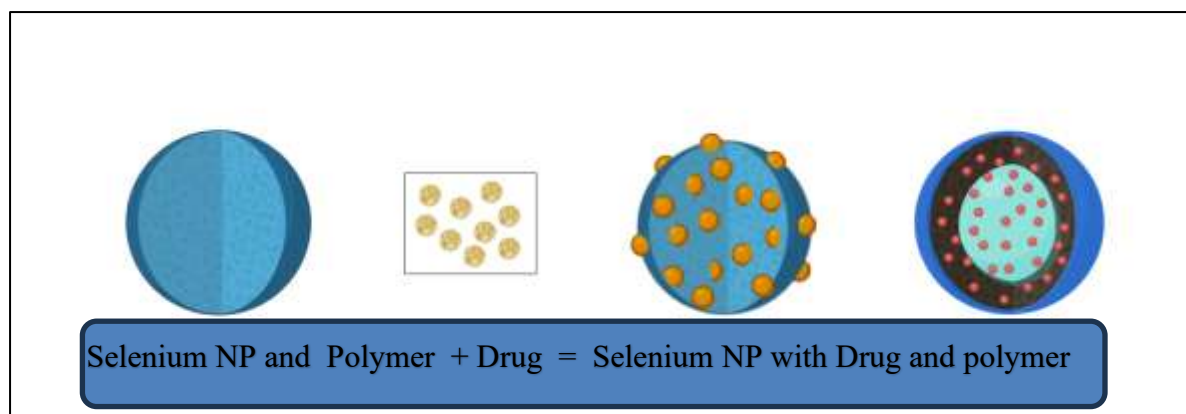


Fig 5: Selenium-based nanoformulation for neurodegenerative diseases.

Selenium nanoparticles stabilized with chitosan and selenium particles stabilized using chitosan and chlorogenic acid: The rationale behind the selection of these combinations was to couple the biocompatibility of chitosan with the antioxidant and metal-chelation properties of chlorogenic acid and silica. Reduction of metal-induced A β formation and DPPH assay were analyzed to determine the potential of this formulation against AD. The formulation was incubated with A β with iron, zinc, and copper individually. Transmission electron microscopy images revealed an A β 1-42 length of 6.3 ± 0.2 nm, whereas, in the presence of iron, fibril width increased to 9.0 ± 0.2 nm. The Selenium nanoparticles stabilized with chitosan reduced fibril width by 20% upon addition to metal-induced A β 1-42 compared to metal-induced A β 1-42 alone. EC50 was determined for DPPH assay, and it revealed that selenium particles stabilized using chitosan and chlorogenic acid had an EC50 of 0.07 ± 0.05 mM. In contrast, selenium nanoparticles stabilized with chitosan showed an EC50 value of 0.9 ± 0.1 mM [5].

Quercetin-loaded selenium nanoparticles coated with acacia and polysorbate 80: Polysorbate 80 was added to enhance the blood-brain barrier permeability as well as to increase the solubility of quercetin. This formulation showed DPPH scavenging activity with an IC50 value of $44 \mu\text{M}$, higher than the well-known antioxidant ascorbic acid ($51 \mu\text{M}$). The nanoformulation was found to inhibit A β 1-42 aggregation by decreasing the fluorescence intensity at 310 nm by quenching the tyrosine residue of A β 1-42. It also possessed higher aqueous solubility compared to quercetin [51].

Selenium-chondroitin sulfate nanoparticles: Chondroitin sulfate (CS) is a compound that exhibits inhibitory potential against neuroinflammation and possesses antioxidant and neuroprotective properties. It can also reduce A β fibril formation and ROS formation. Selenium can decompose pre-formed A β aggregates into nontoxic components as well as inhibit the formation of A β aggregates. The fluorescence intensity observed with A β aggregates was 409.8 ± 7.2 . However, it significantly decreased upon the addition of selenium-chondroitin sulfate nanoparticles to 357.8 ± 9.3 with $50 \mu\text{g/ml}$ and 369.6 ± 6.8 with $25 \mu\text{g/ml}$ concentrations. This results in intensity indicated inhibition of A β 1-42 due to reduced exposure of hydrophobic regions. The nanoformulation inhibited hyperphosphorylation at amino acid residues Ser396 and Ser404 by inhibiting GSK-3 β as analyzed by western blotting [52, 53].

Resveratrol-selenium nanoparticles: Resveratrol suffers from low solubility and low bioavailability in vivo but has neuroprotective properties. Resveratrol-selenium nanoparticles were tested in vivo, and it was revealed that they attenuated impaired oxidative stress and mitochondrial dysfunction. It was also found to increase the levels of acetylcholine in AD mice models upon treatment with nanoparticles compared to the untreated group. The interleukin- β concentration was found to be lower compared to the untreated group. It also down-regulated STAT3 expression, thereby showcasing the potential to treat neuroinflammation. Also, the A β 1-42 concentration was significantly decreased in AD mice that received the formulation compared to the untreated AD mice [53].

Silymarin-encapsulated xanthan-gum stabilized selenium nanocarriers: Silymarin and selenium nanoparticles were fabricated in a single polysaccharide matrix to achieve dual antioxidant and A β disaggregation. The nanocarrier was able to block 90% of DPPH free radicals. Thioflavin T fluorescence assay revealed its ability to cause A β disaggregation, as evidenced by quenched fluorescence intensity. The nanocarriers were also revealed to mitigate A β -induced cytotoxicity[54].

Double selenium nanospheres: Ferroptosis is a regulated cell death phenomenon that is caused by impaired iron metabolism. An adenosine A2A receptor agonist CGS was combined with a double selenium nanoformulation. It

was found to be actively involved in neuronal damage and neuroinflammation associated with AD. It was also shown to transform A β aggregates into A β oligomers by binding to them across a 6-hour time frame at a concentration of 10 μ g/ml. A cellular coumarin-6 fluorescence test was used to measure BBB permeability across HUVEC cells, and it revealed a fluorescence intensity of 98.43% for the nanospheres. The same was confirmed in mice models as the fluorescence intensity of nanospheres reached its peak within 6 to 8 hrs. In vitro, cellular models revealed that the ROS levels in cells treated with A β were up to 80%, whereas, in the cells co-cultured with nanospheres, it decreased to 25%. The nanospheres were found to inhibit cell death and intracellular toxicity by decreasing ROS levels. Mice models revealed an improved memory deficit upon treatment with the formulation. Western blot analysis revealed phosphorylation of amino acid residues serine 196 and 399 and threonine 205 and 231 on tau protein in brain tissue samples with 10 μ g/ml concentration. Mice models also confirmed that it also inhibited ferroptosis at the same concentration [55].

Dual-functional selenium nanoparticles with TGN and LPFFD: LPFFD is a peptide sequence with specificity for a specific domain of the hydrophobic domain of A β . Owing to inefficient BBB permeation, A β inhibitors fail to reach the clinic. Keeping this aspect in mind, TGN, composed of 12 amino acids, was used to enhance BBB permeability. Formulations were prepared in the ratios of LPFFD: TGN as 1:1 (L1T1), 1:2 (L1T2), and 2:1 (L2T1). Then, it was further combined with selenium nanoparticles to achieve a synergistic effect of A β inhibition. The L1T1-selenium nanoparticles were retained in the brain for 24 hrs and showed BBB permeability in vitro. Upon 60 μ g/ml concentration, L1T1-selenium and L2T1-selenium nanoparticles showed a reduction in the fluorescence intensity in the thioflavin T assay by 71% and 75%, respectively. Cell viability was significantly increased by 95% and 98% by L1T1-selenium and L2T1-selenium nanoparticles in PC12 cells. Apoptosis induced by A β was reduced to 8.6% and 3.3% by L1T1-selenium and L2T1-selenium nanoparticles [32].

Epigallocatechin-stabilized selenium nanoparticles coated with Tet-1: Epigallocatechin gallate is known for its potent antioxidant and A β inhibitory activities. Initially, selenium and epigallocatechin gallate nanoparticles were prepared and later coated with Tet-1. Tet-1 is a 12-amino acid long peptide that can efficiently retrograde drug delivery into neuronal cells. A 4% increase in soluble A β was seen upon the addition of epigallocatechin-stabilized selenium nanoparticles coated with Tet-1. The 10 μ g/ml formulation significantly increased cell viability from 0.56 to 0.88 % of controls, indicating the formation of amorphous forms of A β . It also could disaggregate A β into nontoxic forms[56]. In the Knockdown of (SELENOP) SelP from N2A mice, increased sensitivity of neuroblast cells towards A β toxicity was observed in N2A mice. SelP-deficient mice showed deficient learning and deficient long-term potentiation [31]. SelR is essential to maintain redox balance, thereby preventing A β aggregation[57].AD is also associated with endoplasmic reticulum-related stress caused by the presence of A β .

Multifunctional mesoporous of metformin possesses A β scavenging ability as well as increases phagocytosis. However, BBB permeability and short half-life. Transferrin was capable of receptor-mediated endocytosis. Mesoporous nano selenium was loaded with metformin, and surface-coated transferrin was added to enhance BBB permeation. This formulation exhibited broad-range antioxidant activity with efficacy against abnormal ROS and reactive nitrogen species at 50 μ g/ml. It also showed the degradation of A β 1-42 aggregates as well as inhibition of A β 1-42 formation as evidenced by a significant reduction in fluorescence intensity compared to A β 1-42 alone. Cell survival rate upon A β toxicity was 41%, which changed to 90% in the presence of the formulation. Similarly, cell survival due to H₂O₂-induced cytotoxicity was alleviated from 28% to 85%. The formulation reached a maximum fluorescence intensity within 6 hrs, indicating its potential to cross the BBB. In vivo, mice models displayed a beneficial effect on cognition as well as repair of oxidative stress [58].

Sialic acid-modified selenium nanoparticles coated with B6 peptide: Sialic acid is an important component of brain gangliosides that is essential for adequate brain development and cognition. Sialic acid administration in animals was associated with learning and memory performance. B6 peptide was a substitute for transferrin to achieve optimum BBB permeation. Initially, sialic acid-selenium nanoparticles were synthesized, and later, they were coated with B6 peptide. Turbidimetry was used to analyze the effect of the formulation on A β aggregation. It was noted that at 40 μ g/ml, the formulation showed a considerable decrease in turbidity from 0.072 units to 0.042 units, suggesting its role in inhibiting aggregation of A β . It could also transform A β aggregates into amorphous oligomers, showcasing its disaggregation potential [59].

Chondroitin sulfate (CS)-nano selenium: CS proteoglycan plays a key role in learning and memory. CS possesses BACE1 inhibitory potential and thus can control the A β formation. It is also involved in the internalization of tau protein. Overall, it can prevent neurodegeneration. The Mice model revealed that a high dose of the formulation can effectively increase memory and learning function. It afforded neuroprotection against hippocampal neuronal damage induced by aluminum chloride. It also improved cholinergic balance by

enhancing the activity of choline acetyltransferase and suppressing the activity of acetylcholinesterase. It was shown to regulate the excessive phosphorylation of Ser396 and Ser404 present in tau protein by regulating the expression of GSK-3 β . It can also regulate the translocation of NF- κ B, thereby bearing the potential to treat neuroinflammation [60].

Selenium-doped 3D porous molybdenum carbide nanospheres: Mitochondrial dysfunction as a result of oxidative stress is a critical factor in the pathogenesis of AD, which further leads to the formation of ROS. Selenium-doped 3D porous molybdenum carbide nanospheres were employed to promote the antioxidant effect as well as reduce mitochondrial dysfunction. It also displayed a reduction in A β formation, inhibition of overactivated microglia, reduction of proinflammatory factors, and inflammation [61].

Resveratrol-loaded selenium/chitosan nanoflowers: An improper diet can facilitate the risk of AD. Hence, this formulation was developed with the connection between good gut health and AD kept in mind. It aimed to restore the gut bacteria, and it could reduce lipopolysaccharide (LPS) formation and LPS-induced neuroinflammation. It was also found to inhibit A β aggregation and tau hyperphosphorylation. It also significantly enhanced cognitive function in mice [62].

Engineered selenium/Human serum albumin nanoparticles: Human serum albumin (HSA) has good polymer characteristics like non-toxicity, biocompatibility, long half-life, and non-immunogenicity. It can also permeate the BBB via endocytosis and could reach peak concentration in 6 hrs. It suppresses ferroptosis and mitochondrial-related apoptosis. It could also translocate nuclear erythroid factor 2 (Nrf-2) and thereby reduce oxidative stress. It could also improve motor behavior and repair the loss of dopaminergic neurons in mice models [63].

Polydopamine-based nanocomposite co-synthesized with selenocysteine: ROS overproduction and oxidative stress induce neurodegeneration of dopaminergic neurons present in substantia nigra pars compacta. Polydopamine can act as an antioxidant by mimicking the enzymes superoxide dismutase (SOD) and catalase (CAT). Selenocysteine, an essential component of glutathione peroxidase (GPx), was selected for synthesizing the nanocomposite with the aim of inducing GPx-like activity. In the 1-methyl-4-phenyl-pyridine ion (MPP⁺)-induced PD cell model, the formulation showed an increase in GPx activity and protected SH-SY5Y neuronal cells from oxidative stress [64].

Selenium nanoparticles functionalized with polyvinylpyrrolidone (PVP): The nanoparticles were loaded with Levodopa or dopamine, and it was observed that the formulation formed several hydrogen-bonding and/or electrostatic interactions with the compound. These nanoparticles were evidenced to pass the BBB efficiently and thus present a potential alternative for drug delivery of dopamine as therapy for PD with an additional antioxidant effect familiar with selenium [65].

Chiral L-type selenium and ceric oxide nanoparticles: L-cysteine was combined with selenium and ceric oxide to synthesize these nanoparticles. The synergistic effect between selenium and ceric oxide enabled the nanoparticles to reduce the oxidative enzyme activities of peroxidase (POD), CAT, and GPx by 5.6, 7, and 10 times, respectively, compared to their initial reaction velocities. In PD-cell-like models, this formulation showed strong ROS scavenging ability. In the PD mice model, the level of α -synuclein in the cerebrospinal fluid was reduced by about 71% upon two-week therapy [66].

Selenium nanoparticles: *Caenorhabditis elegans* (*C. elegans*) is a classic animal model to replicate and study the effects of treatments against HD. Two types of *C. elegans*- wildtype and transgenic HA759 and AM141 were employed to evaluate the effects of the formulation. Juglone and methylmercury were two chemicals that were used to induce oxidative stress. PolyQ protein is known to be adequately involved in forming aggregates in humans during HD. The formulation under 2 μ M concentration displayed protective effects against both types of stress. Treatment with 0.02, 0.2, and 2 μ M concentrations reduced PolyQ aggregation by 18%, 22%, and 30%, respectively. 2 μ M concentration of the formulation significantly decreased ROS levels of Huntington nematodes. At the same concentration, it could relieve behavioral dysfunction and decrease neuronal death [67].

Table 2. Nano formulations of selenium for neurodegenerative diseases

Summary of Nanoformulation used for Neurodegeneration diseases		
a) Alzheimer's diseases		
Nanoformulations	Molecular targets	Pathological effects
Selenium NP stabilized with chitosan	Formulation incubated with A β with iron, zinc and copper	Selenium nanoparticles stabilized with chitosan reduce fibril width by 20% with EC50 of 0.9 and

	individually.	0.07 mM.
Quercetin -loaded selenium selenium NP coated with acacia and polysorbate 80	To increase blood-brain barrier permeability.	Inhibit A β -42 aggregation. DPPH scavenging activity with IC ₅₀ value of 44 μ M.
Selenium-chondroitin sulfate NP	Antioxidant and neuroprotective properties, reduction of a fibril formation and ROS formation	Inhibited hyperphosphorylation at amino acid residue Ser396 and Ser404 by inhibiting GSK-3 β
Double Selenium nanospheres	Targets Relative oxygen species (ROS)	Inhibiting cell death and intracellular toxicity by decreasing ROS levels. It was shown to transform A β aggregates into A β oligomers by binding to them across six hrs. at a concentration of 10 μ g/ml.
Nanoformulations	Molecular targets	Pathological effects
Silymarin-encapsulated Xanthum -fum stabilized selenium Nanocarriers	Antioxidant and A β disaggregation	Blocked 90% of DPPH free radicals.
Dual-functional selenium nanoparticles with TGN and LPFFD	A β inhibition	Improved BBB and increased retention, due to which 98% A β inhibition was reported.
Resveratrol-selenium nanoparticle	Attenuation impaired oxidative stress and mitochondrial dysfunction.	Increase level of Acetylcholine in AD mice models.
Epigallocatechin-stabilized selenium nanoparticles coated with Tet-1	Potent antioxidant and A β inhibition	Increase in cell viability from 0.56 to 0.88%. Disaggregate A β into nontoxic forms at 10 μ g/ml.
Multifunctional mesoporous nano selenium-loaded metformin	Possesses A β scavenging ability as well as increases phagocytosis	Exhibited broad-range antioxidant activity with efficacy against abnormal ROS and reactive nitrogen Species at 50 μ g/ml.
Sialic acid-modified selenium nanoparticles coated with B6 peptide	Learning and memory performance	Role in inhibiting aggregation of A β at 40 μ g/ml.
Nanoformulations	Molecular targets	Pathological effects
Chondroitin sulfate (CS)- nano selenium	Inhibitory potential and thus can control the A β formation, the internalization of tau protein. Overall, it can prevent neurodegeneration	Effectively increase memory and learning function
Selenium-doped 3D porous molybdenum carbide nanospheres	Promote the antioxidant effect as well as reduce mitochondrial dysfunction.	Reduction of pro-inflammatory factors and inflammation
Resveratrol-loaded selenium/chitosan nanoflowers	Restore the gut bacteria, and it could reduce lipopolysaccharide (LPS) formation and LPS-induced neuroinflammation.	Significantly enhanced cognitive function in mice.
b) Parkinson's disease		

Engineered selenium/Human serum albumin nanoparticles	Suppresses ferroptosis and mitochondrial-related apoptosis	Reduce oxidative stress, improve motor behavior and repair the loss of dopaminergic neurons in mice models.
Nanoformulations	Molecular targets	Pathological effects
Polydopamine-based nanocomposite co-synthesized with selenocysteine	Act as an antioxidant.	An increase in GPx activity and protected SH-SY5Y neuronal cells from oxidative stress
Selenium nanoparticles functionalized with polyvinylpyrrolidone (PVP)	Drug delivery of dopamine as therapy for PD	Additional antioxidant effects familiar with selenium
Chiral L-type selenium and ceric oxide nanoparticles	Reduction of the oxidative enzyme activities of peroxidase (POD),	Showed strong ROS scavenging ability
c) Huntington's disease		
Selenium nanoparticles	Decreasing Neuronal Death.	0.02 to 2 μ M concentration reduced PolyQ aggregation up to 18% to 30%. 2 μ M concentration decreases ROS levels.

Discussion:

Understanding the role of selenium in the progression of neurodegenerative disorders is in its primary stage. Selenium and selenoproteins are known to be essential for normal brain development and significantly contribute to memory and learning. Many underlying mechanisms are proposed, starting from their role in ROS scavenging to the involvement of Se in protein misfolding and protein aggregation, and they are validated by carrying out the experimental study. Dietary intake and cellular redox state influence the regulation of selenoprotein expression by selenium availability. Selenoproteins play a positive role in combating human diseases such as Alzheimer's, Parkinson's, multiple sclerosis, schizophrenia, and mood disorders. Now, we are at the stage of understanding the role of Se-based nanoformulations in the reduction of A β 1-42 aggregation. Selenium-chondroitin sulfate nanoparticles not only inhibit hyperphosphorylation of amino acid residue Ser396 and Ser404 by inhibiting GSK-3 β but also increase the level of acetylcholine, downregulating STAT3 expression involved in neuroinflammation. Chondroitin sulfate (CS)-Nano selenium enhances the choline acetyltransferase activity. In Parkinson's disease, nanoformulations showed an increase in GPx activity and protected SH-SY5Y neuronal cells from oxidative stress. Selenium nanoparticles, with PVP, have shown potential alternative for the drug delivery of dopamine with additional antioxidant activity. Various experimental evidence suggests the role of selenium supplementation in the progression of neurodegenerative disorders in a dose-dependent manner. Their role in neurogenesis, size, shape, and number of neurospheres is now clearly established. The inclusion of selenium in the diet may have therapeutic interventions that have beneficial effects on cognitive functions, protein aggregation and misfolding, and neurogenesis. Elderly individuals could easily increase their intake of selenium because it is an inexpensive, easily accessible dietary supplement that is present in many regularly consumed foods, including dairy products, cereals, and nuts. This is especially crucial for the care of those who are too old, too fragile, or disabled to exercise.

Research conducted by various groups shed some light on the basic understanding of the correlation between Se and its role in neuroprotection. We hereby summarize the various future studies essential for a better understanding of molecular mechanisms underlying the topic under consideration.

1. Selenoproteins F is important in ensuring proper protein folding and secretion. Given its involvement in critical cellular processes, further research into SeF could provide insights into its potential as a biomarker or therapeutic target for various diseases.
2. Understanding the interplay between selenium, selenoproteins, and alpha-synuclein accumulation could provide insights into PD mechanisms. This relationship may also present potential therapeutic avenues, such as selenium supplementation or targeting specific selenoproteins to alleviate symptoms or slow disease progression.
3. Selenoproteins are vital for maintaining cellular homeostasis and protecting against disease. Their regulation is complex and influenced by multiple factors, making them important players in the pathology of various human diseases. Ongoing research is needed to fully elucidate their roles and potential therapeutic applications.
4. Selenium and selenoproteins are vital for maintaining brain health through their antioxidant, anti-inflammatory, and neuroprotective roles. Dysregulation of selenium levels and selenoproteins' function has been implicated in various brain diseases, highlighting their potential as therapeutic targets for prevention and

treatment. Ongoing research is needed to elucidate these relationships further and develop strategies for enhancing selenium status in the context of brain health.

5. The ER system plays a vital role in preventing the formation of neurofibrillary tangles by facilitating proper protein folding, regulating cellular stress responses, maintaining calcium homeostasis, and supporting autophagy. Enhancing ER function and addressing ER stress may offer potential therapeutic strategies for neurodegenerative diseases characterized by tau pathology.

6. More research is needed to understand the molecular mechanism of selenium supplementation in depth that could have therapeutic benefits in neurodegenerative disorders.

7. On our part, considering the studies involving Se-based nanoformulations, we recommend investigating the combination of Acetylcholinesterase (AChE) inhibitors or Dopamine agonists with Se-based formulations for the treatment of Alzheimer's disease or Parkinson's disease. A recent study involving the fusion of donepezil, an AChE inhibitor, and Ebselen, a potent organoselenium anti-inflammatory cytoprotective agent, led to the development of a series of organoselenium was carried out, and out of the many derivatives synthesized, around 10 selenoderivatives exhibited potent effect with IC₅₀ values reaching submicromolar concentration when tested for their AChE inhibition. Similar effects were observed with inhibition of Butyrylcholinesterase (BuChE); this suggests the positive role of selenium-containing motifs in cognitive deficits related to neurodegenerative diseases [68][69, 70]. Furthermore, the study also involves the examination of the most potent analog in the series, selenepzil. The mentioned analog was found to be an inhibitor of human GPx-like activity, was found nontoxic when administered to mice [68], and demonstrated a neuroprotective effect against 6-hydroxydopamine (6-OHDA) or H₂O₂-induced SH-SY5Y cell damage through activation of Keap-1-Nrf-2 ARE signaling pathway, its administration also found ameliorating Aβ-induced cognitive impairment in-vivo [68].

Conclusion:

The emergence of neurodegenerative disorders in the later stages of life is a significant concern in recent times. Therefore, there is an urgent need to test the efficacy of Se-based nanoformulations in the progression of neurodegeneration. Such studies have already been initiated and must be carried forward. With the help of modern drug discovery tools, molecular interactions between the Se and protein misfolding, aggregation, and neurodegeneration can certainly lead us to a better understanding. Being a metal, it is also essential to conduct well-planned toxicity studies involving Se-based nanoformulations. The authors wish to suggest the study of the binding pattern of Se in the synthesis of proteins like Aβ, alpha-synuclein, and their folding. Further, pharmacokinetic and pharmacodynamic studies involving Se-based combinations of well-known drugs in the treatment of AD, PD, and HD suggest that synergistic roles should be undertaken. This will help us design new molecules in the future to control the progression occurrence or treatment of various neurodegenerative disorders. There is a titanic scope for evaluating the mechanisms of Se-based nanoformulations in neuroprotection by utilizing the proposed combinations. This will open up a new dimension in the research associated with neurodegeneration.

Statement and Declaration:

Clinical Trial Number: not applicable

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of Interest: The authors declare no conflict of interest.

Authors' Contributions: Dhara Pandey wrote the main manuscript and prepared figures and a table. Dr. Kunal Gokhale reviewed the manuscript. All the data were generated in-house, and no paper mill was used. All authors read, reviewed, and approved the manuscript.

Acknowledgment: The Authors are thankful to Nachiket Joshi for his valuable contributions.

Reference:

1. Gustavsson, Anders, Nicholas Norton, Thomas Fast, Lutz Frölich, Jean Georges, Drew Holzapfel, Tunahan Kirabali, et al. 2023. Global estimates on the number of persons across the Alzheimer's disease continuum. *Alzheimer's & dementia: the journal of the Alzheimer's Association* 19. *Alzheimers Dement*: 658–670. <https://doi.org/10.1002/ALZ.12694>.
2. Medina, Alex, Yasamin Mahjoub, Larry Shaver, and Tamara Pringsheim. 2022. Prevalence and Incidence of Huntington's Disease: An Updated Systematic Review and Meta-Analysis. *Movement disorders: official journal of the Movement Disorder Society* 37. *Mov Disord*: 2327–2335. <https://doi.org/10.1002/MDS.29228>.
3. Shahidin, Yan Wang, Yilong Wu, Taixia Chen, Xiaoyun Wu, Wenjuan Yuan, Qiangqiang Zhu, Xuanjun

- Wang, and Chengting Zi. 2025. Selenium and Selenoproteins: Mechanisms, Health Functions, and Emerging Applications. *Molecules* 30: 1–35. <https://doi.org/10.3390/molecules30030437>.
4. Cardoso, Bárbara R., Dominic J. Hare, and Ashley I. Bush. 2017. The Role of Selenium in Neurodegenerative Diseases. *Biometals in Neurodegenerative Diseases: Mechanisms and Therapeutics*. Academic Press: 35–49. <https://doi.org/10.1016/B978-0-12-804562-6.00003-8>.
 5. Vicente-Zurdo, David, Iván Romero-Sánchez, Noelia Rosales-Conrado, María Eugenia León-González, and Yolanda Madrid. 2020. Ability of selenium species to inhibit metal-induced A β aggregation involved in the development of Alzheimer's disease. *Analytical and bioanalytical chemistry* 412. *Anal Bioanal Chem*: 6485–6497. <https://doi.org/10.1007/S00216-020-02644-2>.
 6. Lamptey, Richard N.L., Bivek Chaulagain, Riddhi Trivedi, Avinash Gothwal, Buddhadev Layek, and Jagdish Singh. 2022. A Review of the Common Neurodegenerative Disorders: Current Therapeutic Approaches and the Potential Role of Nanotherapeutics. *International journal of molecular sciences* 23. *Int J Mol Sci*. <https://doi.org/10.3390/IJMS23031851>.
 7. Wilson, David M., Mark R. Cookson, Ludo Van Den Bosch, Henrik Zetterberg, David M. Holtzman, and Ilse Dewachter. 2023. Hallmarks of neurodegenerative diseases. *Cell* 186. *Cell*: 693–714. <https://doi.org/10.1016/J.CELL.2022.12.032>.
 8. Dugger, Brittany N., and Dennis W. Dickson. 2017. Pathology of Neurodegenerative Diseases. *Cold Spring Harbor perspectives in biology* 9. *Cold Spring Harb Perspect Biol*. <https://doi.org/10.1101/CSHPERSPECT.A028035>.
 9. Guo, Tiantian, Denghong Zhang, Yuzhe Zeng, Timothy Y. Huang, Huaxi Xu, and Yingjun Zhao. 2020. Molecular and cellular mechanisms underlying the pathogenesis of Alzheimer's disease. *Molecular neurodegeneration* 15. *Mol Neurodegener*. <https://doi.org/10.1186/S13024-020-00391-7>.
 10. Rostagno, Agueda A. 2022. Pathogenesis of Alzheimer's Disease. *International journal of molecular sciences* 24. *Int J Mol Sci*. <https://doi.org/10.3390/IJMS24010107>.
 11. Tiwari, Sneham, Venkata Atluri, Ajeet Kaushik, Adriana Yndart, and Madhavan Nair. 2019. Alzheimer's disease: pathogenesis, diagnostics, and therapeutics. *International journal of nanomedicine* 14. *Int J Nanomedicine*: 5541–5554. <https://doi.org/10.2147/IJN.S200490>.
 12. Breijyeh, Zeinab, and Rafik Karaman. 2020. Comprehensive Review on Alzheimer's Disease: Causes and Treatment. *Molecules (Basel, Switzerland)* 25. *Molecules*. <https://doi.org/10.3390/MOLECULES25245789>.
 13. Chen, Zhi Ru, Jia Bao Huang, Shu Long Yang, and Fen Fang Hong. 2022. Role of Cholinergic Signaling in Alzheimer's Disease. *Molecules (Basel, Switzerland)* 27. *Molecules*. <https://doi.org/10.3390/MOLECULES27061816>.
 14. Aryal, Sunisha, Taylor Skinner, Bronwyn Bridges, and John T. Weber. 2020. The Pathology of Parkinson's Disease and Potential Benefit of Dietary Polyphenols. *Molecules (Basel, Switzerland)* 25. *Molecules*. <https://doi.org/10.3390/MOLECULES25194382>.
 15. MacMahon Copas, Adina N., Sarah F. McComish, Jean M. Fletcher, and Maeve A. Caldwell. 2021. The Pathogenesis of Parkinson's Disease: A Complex Interplay Between Astrocytes, Microglia, and T Lymphocytes? *Frontiers in neurology* 12. *Front Neurol*. <https://doi.org/10.3389/FNEUR.2021.666737>.
 16. Woerman, Amanda L., Joel C. Watts, Atsushi Aoyagi, Kurt Giles, Lefkos T. Middleton, and Stanley B. Prusiner. 2018. A-synuclein: Multiple system atrophy prions. *Cold Spring Harbor Perspectives in Medicine* 8: 1–12. <https://doi.org/10.1101/cshperspect.a024588>.
 17. Jimenez-Sanchez, Maria, Floriana Licitra, Benjamin R. Underwood, and David C. Rubinsztein. 2017. Huntington's Disease: Mechanisms of Pathogenesis and Therapeutic Strategies. *Cold Spring Harbor perspectives in medicine* 7. *Cold Spring Harb Perspect Med*: 1–22. <https://doi.org/10.1101/CSHPERSPECT.A024240>.
 18. 2023 Alzheimer's disease facts and figures. 2023. *Alzheimer's & dementia : the journal of the Alzheimer's Association* 19. *Alzheimers Dement*: 1598–1695. <https://doi.org/10.1002/ALZ.13016>.
 19. Bhat, Shahnawaz Ali, Shakir Ahamad, Nawab John Dar, Yasir Hassan Siddique, and Aamir Nazir. 2023. The Emerging Landscape of Natural Small-molecule Therapeutics for Huntington's Disease. *Current neuropharmacology* 21. *Curr Neuropharmacol*: 867–889. <https://doi.org/10.2174/1570159X21666230216104621>.
 20. Hariharan, Sneha, and Selvakumar Dharmaraj. 2020. Selenium and selenoproteins: it's role in regulation of inflammation. *Inflammopharmacology* 28. *Inflammopharmacology*: 667–695. <https://doi.org/10.1007/S10787-020-00690-X>.
 21. Yang, Licong, Jing Sun, Wenjie Xie, Yanan Liu, and Jie Liu. 2017. Dual-functional selenium nanoparticles bind to and inhibit amyloid β fiber formation in Alzheimer's disease. *Journal of materials chemistry. B* 5. *J Mater Chem B*: 5954–5967. <https://doi.org/10.1039/C6TB02952C>.
 22. Bellinger, Frederick P., Arjun V. Raman, Mariclaire A. Reeves, and Marla J. Berry. 2009. Regulation and function of selenoproteins in human disease. *The Biochemical journal* 422: 11. <https://doi.org/10.1042/BJ20090219>.
 23. Minich, Waldemar B. 2022. Selenium Metabolism and Biosynthesis of Selenoproteins in the Human Body.

- Biochemistry (Moscow) 87: S168–S177.
<https://doi.org/10.1134/S0006297922140139>.
24. Short, Sarah P., and Christopher S. Williams. 2017. Selenoproteins in Tumorigenesis and Cancer Progression. *Advances in Cancer Research* 136: 49–83.
<https://doi.org/10.1016/bs.acr.2017.08.002>.
25. Casanova, Pilar, and Daniel Monleon. 2023. Role of selenium in type 2 diabetes, insulin resistance and insulin secretion. *World Journal of Diabetes* 14: 147–158.
<https://doi.org/10.4239/wjd.v14.i3.147>.
26. Ding, Wenqiang, Shuang Wang, Jiayang Gu, and Lei Yu. 2023. Selenium and human nervous system. *Chinese Chemical Letters* 34. Elsevier: 108043.
<https://doi.org/10.1016/J.CCLET.2022.108043>.
27. Zhang, Xiong, Rong Pei Liu, Wen Hsing Cheng, and Jian Hong Zhu. 2019. Prioritized brain selenium retention and selenoprotein expression: Nutritional insights into Parkinson’s disease. *Mechanisms of Ageing and Development* 180. Elsevier: 89–96.
<https://doi.org/10.1016/J.MAD.2019.04.004>.
28. Chen, Jun, and Marla J. Berry. 2003. Selenium and selenoproteins in the brain and brain diseases. *Journal of neurochemistry* 86. *J Neurochem*: 1–12. <https://doi.org/10.1046/J.1471-4159.2003.01854.X>.
29. Hertzog da Silva Leme, Adriana Gisele, and Barbara R. Cardoso. 2020. Selenium and Alzheimer’s disease. *Genetics, Neurology, Behavior, and Diet in Dementia: The Neuroscience of Dementia, Volume 2*. Academic Press: 739–748. <https://doi.org/10.1016/B978-0-12-815868-5.00047-5>.
30. Ren, Bingyu, Min Liu, Jiazuan Ni, and Jing Tian. 2018. Role of Selenoprotein F in Protein Folding and Secretion: Potential Involvement in Human Disease. *Nutrients* 10. *Nutrients*.
<https://doi.org/10.3390/NU10111619>.
31. Pillai, Roshan, Jane H. Uyehara-Lock, and Frederick P. Bellinger. 2014. Selenium and selenoprotein function in brain disorders. *IUBMB life* 66. *IUBMB Life*: 229–239. <https://doi.org/10.1002/IUB.1262>.
32. Yang, Licong, Jing Sun, Wenjie Xie, Yanan Liu, and Jie Liu. 2017. Dual-functional selenium nanoparticles bind to and inhibit amyloid β fiber formation in Alzheimer’s disease. *Journal of materials chemistry. B* 5. *J Mater Chem B*: 5954–5967.
<https://doi.org/10.1039/C6TB02952C>.
33. Solovyev, Nikolay D. 2015. Importance of selenium and selenoprotein for brain function: From antioxidant protection to neuronal signalling. *Journal of inorganic biochemistry* 153. *J Inorg Biochem*: 1–12. <https://doi.org/10.1016/J.JINORGBIO.2015.09.003>.
34. Bodnár, Dóra, Olga Ruzsnavszky, Tamás Oláh, Beatrix Dienes, Ildikó Balatoni, Éva Ungvári, Ilona Benkő, et al. 2016. Dietary selenium augments sarcoplasmic calcium release and mechanical performance in mice. *Nutrition & metabolism* 13. *Nutr Metab (Lond)*: 1–13. <https://doi.org/10.1186/S12986-016-0134-6>.
35. Ramachandran, Anu Kunnath, Subham Das, Alex Joseph, Gurupur Gautham Shenoy, Angel Treasa Alex, and Jayesh Mudgal. 2021. Neurodegenerative Pathways in Alzheimer’s Disease: A Review. *Current Neuropharmacology* 19. Bentham Science Publishers Ltd.: 679.
<https://doi.org/10.2174/1570159X18666200807130637>.
36. Zielińska, Magdalena, Edyta Łuszczki, and Katarzyna Dereń. 2023. Dietary Nutrient Deficiencies and Risk of Depression (Review Article 2018–2023). *Nutrients* 15. <https://doi.org/10.3390/nu15112433>.
37. Akbaraly, N. Tasnime, Isabelle Hininger-Favier, Isabelle Carrière, Josiane Arnaud, Veronique Gourlet, Anne Marie Roussel, and Claudine Berr. 2007. Plasma selenium over time and cognitive decline in the elderly. *Epidemiology (Cambridge, Mass.)* 18. *Epidemiology*: 52–58.
<https://doi.org/10.1097/01.EDE.0000248202.83695.4E>.
38. Cardoso, Bárbara Rita, Blaine R. Roberts, Ashley I. Bush, and Dominic J. Hare. 2015. Selenium, selenoproteins and neurodegenerative diseases. *Metallomics : integrated biometal science* 7. *Metallomics*: 1213–1228. <https://doi.org/10.1039/C5MT00075K>.
39. Leiter, Odette, Zhan Zhuo, Ruslan Rust, Joanna M. Wasielewska, Lisa Grönnert, Susann Kowal, Rupert W. Overall, et al. 2022. Selenium mediates exercise-induced adult neurogenesis and reverses learning deficits induced by hippocampal injury and aging. *Cell metabolism* 34. *Cell Metab*: 408-423.e8.
<https://doi.org/10.1016/J.CMET.2022.01.005>.
40. Leiter, Odette, Zhan Zhuo, Ruslan Rust, Joanna M. Wasielewska, Lisa Grönnert, Susann Kowal, Rupert W. Overall, et al. 2022. Selenium mediates exercise-induced adult neurogenesis and reverses learning deficits induced by hippocampal injury and aging. *Cell metabolism* 34. *Cell Metab*: 408-423.e8.
<https://doi.org/10.1016/J.CMET.2022.01.005>.
41. Barchielli, Giulia, Antonella Capperucci, and Damiano Tanini. 2022. The Role of Selenium in Pathologies: An Updated Review. *Antioxidants (Basel, Switzerland)* 11. *Antioxidants (Basel)*.
<https://doi.org/10.3390/ANTIOX11020251>.
42. Du, Xiubo, Chao Wang, and Qiong Liu. 2016. Potential Roles of Selenium and Selenoproteins in the

- Prevention of Alzheimer's Disease. Current topics in medicinal chemistry 16. *Curr Top Med Chem*: 835–848. <https://doi.org/10.2174/1568026615666150827094936>.
43. Solovyev, Nikolay, Evgenii Drobyshev, Geir Bjørklund, Yaroslav Dubrovskii, Roman Lysiuk, and Margaret P. Rayman. 2018. Selenium, selenoprotein P, and Alzheimer's disease: is there a link? *Free radical biology & medicine* 127. *Free Radic Biol Med*: 124–133. <https://doi.org/10.1016/J.FREERADBIOMED.2018.02.030>.
44. Cardoso, Bárbara Rita, Blaine R. Roberts, Ashley I. Bush, and Dominic J. Hare. 2015. Selenium, selenoproteins and neurodegenerative diseases. *Metallomics : integrated biometal science* 7. *Metallomics*: 1213–1228. <https://doi.org/10.1039/C5MT00075K>.
45. Ellwanger, Joel H., Silvia I.R. Franke, Diana L. Bordin, Daniel Prá, and João Antonio Pêgas Henriques. 2016. Biological functions of selenium and its potential influence on Parkinson's disease. *Anais da Academia Brasileira de Ciências* 88. *An Acad Bras Cienc*: 1655–1674. <https://doi.org/10.1590/0001-3765201620150595>.
46. Salaramoli, Sanaz, Hamid Reza Joshaghani, Ali Shoeibi, and Seyed Isaac Hashemy. 2024. Selenium and selenoproteins role in Parkinson's disease: Is there a link between selenoproteins and accumulated alpha-synuclein? *Journal of trace elements in medicine and biology : organ of the Society for Minerals and Trace Elements (GMS)* 81. *J Trace Elem Med Biol*. <https://doi.org/10.1016/J.JTEMB.2023.127344>.
47. Zeng, Zhaohao, Yanmei Cen, and Xiaoguang Luo. 2023. Association between blood selenium with parkinson's disease in the US (NHANES 2011-2020). *Environmental science and pollution research international* 30. *Environ Sci Pollut Res Int*: 117349–117359. <https://doi.org/10.1007/S11356-023-30337-7>.
48. Johri, Ashu, and M. Flint Beal. 2012. Antioxidants in Huntington's disease. *Biochimica et biophysica acta* 1822. *Biochim Biophys Acta*: 664–674. <https://doi.org/10.1016/J.BBADIS.2011.11.014>.
49. Bicca Obetine Baptista, Fabiane, Leticia Priscilla Arantes, Marina Lopes Machado, Aline Franzen Da Silva, Larissa Marafiga Cordeiro, Tássia Limana Da Silveira, and Felix Alexandre Antunes Soares. 2020. Diphenyl diselenide protects a *Caenorhabditis elegans* model for Huntington's disease by activation of the antioxidant pathway and a decrease in protein aggregation. *Metallomics : integrated biometal science* 12. *Metallomics*: 1142–1158. <https://doi.org/10.1039/D0MT00074D>.
50. Browne, Susan E., Robert J. Ferrante, and M. Flint Beal. 1999. Oxidative stress in Huntington's disease. *Brain pathology (Zurich, Switzerland)* 9. *Brain Pathol*: 147–163. <https://doi.org/10.1111/J.1750-3639.1999.TB00216.X>.
51. Qi, Yujie, Pengji Yi, Ting He, Xianwen Song, Yilin Liu, Qiang Li, Jun Zheng, et al. 2020. Quercetin-loaded selenium nanoparticles inhibit amyloid- β aggregation and exhibit antioxidant activity. *Colloids and Surfaces A: Physicochemical and Engineering Aspects* 602. Elsevier: 125058. <https://doi.org/10.1016/J.COLSURFA.2020.125058>.
52. Gao, Fei, Jing Zhao, Ping Liu, Dongsheng Ji, Litao Zhang, Mengxiao Zhang, Yuqin Li, and Yuliang Xiao. 2020. Preparation and in vitro evaluation of multi-target-directed selenium-chondroitin sulfate nanoparticles in protecting against the Alzheimer's disease. *International Journal of Biological Macromolecules* 142. Elsevier: 265–276. <https://doi.org/10.1016/J.IJBIOMAC.2019.09.098>.
53. Abozaid, Omayma A.R., Mohsen W. Sallam, Sawsan El-Sonbaty, Samy Aziza, Basma Emad, and Esraa S.A. Ahmed. 2022. Resveratrol-Selenium Nanoparticles Alleviate Neuroinflammation and Neurotoxicity in a Rat Model of Alzheimer's Disease by Regulating Sirt1/miRNA-134/GSK3 β Expression. *Biological trace element research* 200. *Biol Trace Elem Res*: 5104–5114. <https://doi.org/10.1007/S12011-021-03073-7>.
54. Saini, Vanshul, Ajit Singh, Rahul Shukla, Keerti Jain, and A. K. Yadav. 2022. Silymarin-Encapsulated Xanthan Gum-Stabilized Selenium Nanocarriers for Enhanced Activity Against Amyloid Fibril Cytotoxicity. *AAPS PharmSciTech* 23. *AAPS PharmSciTech*. <https://doi.org/10.1208/S12249-022-02274-0>.
55. Wang, Jingyuan, Zekun Wang, Yuqing Li, Yajun Hou, Chenyang Yin, Endong Yang, Ziyu Liao, Cundong Fan, Lisandra L. Martin, and Dongdong Sun. 2023. Blood brain barrier-targeted delivery of double selenium nanospheres ameliorates neural ferroptosis in Alzheimer's disease. *Biomaterials* 302. *Biomaterials*. <https://doi.org/10.1016/J.BIOMATERIALS.2023.122359>.
56. Zhang, Jingnan, Xianbo Zhou, Qianqian Yu, Licong Yang, Dongdong Sun, Yanhui Zhou, and Jie Liu. 2014. Epigallocatechin-3-gallate (EGCG)-stabilized selenium nanoparticles coated with Tet-1 peptide to reduce amyloid- β aggregation and cytotoxicity. *ACS applied materials & interfaces* 6. *ACS Appl Mater Interfaces*: 8475–8487. <https://doi.org/10.1021/AM501341U>.
57. Du, Xiubo, Chao Wang, and Qiong Liu. 2016. Potential Roles of Selenium and Selenoproteins in the Prevention of Alzheimer's Disease. Current topics in medicinal chemistry 16. *Curr Top Med Chem*: 835–848. <https://doi.org/10.2174/1568026615666150827094936>.
58. Guo, Xian, Borui Zhang, Ran Tang, Yutong Chen, Ji an Wei, Zhi Jia, Xiaoyu Yuan, Li Zhang, and Jie Liu. 2022. Mesoporous Nanoselenium-Loaded Metformin Delivers Through Bbb to Ameliorate Alzheimer's Disease by Reducing Oxidative Stress and Mediating Microglia Activation. *SSRN Electronic Journal*. Elsevier BV. <https://doi.org/10.2139/SSRN.4112737>.

59. Zheng, Jun Sheng, Shan Yuan Zheng, Yi Bo Zhang, Bo Yu, Wenjie Zheng, Fang Yang, and Tianfeng Chen. 2011. Sialic acid surface decoration enhances cellular uptake and apoptosis-inducing activity of selenium nanoparticles. *Colloids and surfaces. B, Biointerfaces* 83. *Colloids Surf B Biointerfaces*: 183–187. <https://doi.org/10.1016/J.COLSURFB.2010.11.023>.
60. Ji, Dongsheng, Xiaming Wu, Delong Li, Ping Liu, Sitao Zhang, Debo Gao, Fei Gao, Mengxiao Zhang, and Yuliang Xiao. 2020. Protective effects of chondroitin sulphate nano-selenium on a mouse model of Alzheimer's disease. *International journal of biological macromolecules* 154. *Int J Biol Macromol*: 233–245. <https://doi.org/10.1016/J.IJBIOMAC.2020.03.079>.
61. Cai, Qianyu, Xian Guo, Yutong Chen, Jie Liu, and Yanan Liu. 2023. Selenium-Doped 3D Porous Molybdenum Carbide Nanospheres Improve Mitochondrial Function by Reducing Oxidative Stress in Alzheimer's Disease. *ACS Applied Nano Materials* 6. American Chemical Society: 22496–22505. https://doi.org/10.1021/ACSANM.3C05296/ASSET/IMAGES/MEDIUM/AN3C05296_0010.GIF.
62. Yang, Licong, Yabin Wang, Guodong Zheng, Zhiwei Li, and Jingtao Mei. 2023. Resveratrol-loaded selenium/chitosan nano-flowers alleviate glucolipid metabolism disorder-associated cognitive impairment in Alzheimer's disease. *International journal of biological macromolecules* 239. *Int J Biol Macromol*. <https://doi.org/10.1016/J.IJBIOMAC.2023.124316>.
63. Xu, Kai, Peng Huang, Yixuan Wu, Teng Liu, Ningyi Shao, Lulu Zhao, Xiaoyan Hu, Junlei Chang, Yongbo Peng, and Shaogang Qu. 2023. Engineered Selenium/Human Serum Albumin Nanoparticles for Efficient Targeted Treatment of Parkinson's Disease via Oral Gavage. *ACS nano* 17. *ACS Nano*: 19961–19980. <https://doi.org/10.1021/ACSANO.3C05011>.
64. Wang, Wei, Jinyang Zheng, Hao Zhou, Qiang Liu, Li Jia, Xiuming Zhang, Dongtao Ge, Wei Shi, and Yanan Sun. 2022. Polydopamine-Based Nanocomposite as a Biomimetic Antioxidant with a Variety of Enzymatic Activities for Parkinson's Disease. *ACS applied materials & interfaces* 14. *ACS Appl Mater Interfaces*: 32901–32913. <https://doi.org/10.1021/ACSAMI.2C06981>.
65. Kalčec, Nikolina, Nikolina Peranić, Ivan Mamić, Maja Beus, Christopher R. Hall, Trevor A. Smith, Marc Antoine Sani, Petra Turčić, Frances Separovic, and Ivana Vinković Vrček. 2023. Selenium Nanoparticles as Potential Drug-Delivery Systems for the Treatment of Parkinson's Disease. *ACS Applied Nano Materials* 6. American Chemical Society: 17581–17592. <https://doi.org/10.1021/ACSANM.3C02749>.
66. Liu, Ximing, Hongyu Zhang, Changlong Hao, Hua Kuang, Chuanlai Xu, and Liguang Xu. 2023. Chiral Se@CeO₂ superparticles for ameliorating Parkinson's disease. *Nanoscale* 15. *Nanoscale*: 4367–4377. <https://doi.org/10.1039/D2NR04534F>.
67. Cong, Wenshu, Ru Bai, Yu Feng Li, Liming Wang, and Chunying Chen. 2019. Selenium Nanoparticles as an Efficient Nanomedicine for the Therapy of Huntington's Disease. *ACS applied materials & interfaces* 11. *ACS Appl Mater Interfaces*: 34725–34735. <https://doi.org/10.1021/ACSAMI.9B12319>.
68. Yan, Jun, Yanqing Pang, Jialing Zhuang, Haibiao Lin, Qiaoxuan Zhang, Liqiao Han, Peifeng Ke, Junhua Zhuang, and Xianzhang Huang. 2019. Selenepzil, a Selenium-Containing Compound, Exerts Neuroprotective Effect via Modulation of the Keap1-Nrf2-ARE Pathway and Attenuates A β -Induced Cognitive Impairment in Vivo. *ACS chemical neuroscience* 10. *ACS Chem Neurosci*: 2903–2914. <https://doi.org/10.1021/ACSCHEMNEURO.9B00106>.
69. Morán-Serradilla, Cristina, Daniel Plano, Carmen Sanmartín, and Arun K. Sharma. 2024. Selenization of Small Molecule Drugs: A New Player on the Board. *Journal of medicinal chemistry* 67. *J Med Chem*: 7759–7787. <https://doi.org/10.1021/ACS.JMEDCHEM.3C02426>.
70. Luo, Zonghua, Jianfei Sheng, Yang Sun, Chuanjun Lu, Jun Yan, Anqiu Liu, Hai Bin Luo, Ling Huang, and Xingshu Li. 2013. Synthesis and evaluation of multi-target-directed ligands against Alzheimer's disease based on the fusion of donepezil and ebselen. *Journal of medicinal chemistry* 56. *J Med Chem*: 9089–9099. <https://doi.org/10.1021/JM401047Q>.