Chapter

Emerging Selenium Nanoparticles for CNS Intervention

Jonaid Ahmad Malik, Jeba AjgarAnsari, Sakeel Ahmed, Archana Rani, Shabana Yasmeen Ansari and Sirajudheen Anwar

Abstract

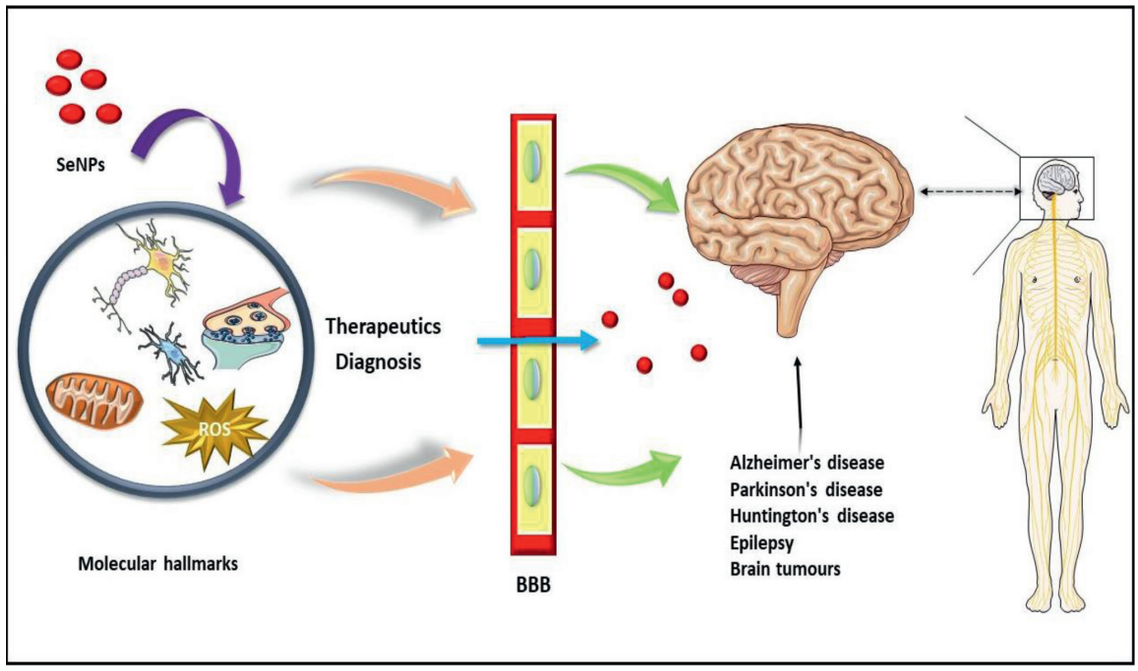
Central nervous system (CNS) diseases have seriously impacted human wellness for the past few decades, specifically in developing countries, due to the unavailability of successful treatment. Due to the blood-brain barrier (BBB) and blood-cerebrospinal fluid barrier transport of drug and treatment of CNS disorders has become difficult. Nanoscale materials like Selenium nanoparticles (SeNPs) offer a possible therapeutic strategy for treating brain diseases like Alzheimer's, Frontotemporal dementia, Amyotrophic lateral sclerosis, Epilepsy, Parkinson's disease, and Huntington's disease. After being functionalized with active targeting ligands, SeNPs are versatile and competent in conveying combinations of cargoes to certain targets. We shall pay close attention to the primarily targeted therapies for SeNPs in CNS diseases. The objective of this paper was to highlight new developments in the exploration of SeNP formation and their potential applications in the management of CNS diseases. Furthermore, we also discussed the mechanisms underlying management of CNS disease, several therapeutic potentials for SeNPs, and the results of their preclinical research using diverse animal models. These methods might lead to better clinical and diagnostic results.

Keywords: selenium, nanoparticles, CNS diseases

1. Introduction

The central nervous disordersare progressive degeneration of neurons in the central nervous system, which results in altered brain cellular function. The major symptoms begin from degeneration of neurons to loss of coordination and memory and ultimately result in complete loss of function in healthy individuals. The three crucial neurodegenerative disorders (NDs) have been recognized as Alzheimer's disease (AD), Parkinson's disease (PD), and Amyotrophic lateral sclerosis (ALS) [1], affecting millions of individuals worldwide. AD is one of the most prevalent NDs and has affected mostly 30% of the aged people [2]. The second most common neurodegenerative disorder is PD, which affects 10–15 individuals per 100,000 people yearly [3]. It is estimated that PD cases will increase worldwide and may cross 12 million cases in 2050 [4]. Similarly, cases of ALS are also increasing with 1–2.6 new cases per

100,000 persons. The average age of onset of this disease is 59–60 years, and the average time from diagnosis to death is 3–4 years [5]. Besides these disorders, Gliomas, and glioblastoma, intrinsic brain tumors arise from neuroglial cells [6].



Other disorders include Huntington's disease (HD), depression, anxiety, autism spectrum disorders, seizures, etc. [7]. The establishment of innovative NDs treatments are urgently needed as the WHO has predicted that within the next 20 years NDs will surpass cancer and will become the second most common cause of death [8]. Natural products may offer great promises compared to classical therapies available to improve the symptoms but cannot prevent their progression. Therefore, researchers are continuously searching for new natural products that can potentially treat NDs without compromising the patient's health. However, all-natural products are not always safe; because natural products as drugs may have more adverse effects than their benefits as they are derived from various biological sources, their conversion into therapeutic formulations may face many hurdles such as safety issues, difficulty in identifying active ingredients because natural products contain various active phytochemicals such as flavonoids, alkaloids, etc. And it becomes difficult to identify which components of the herb have maximum therapeutic potential, low stability and high degradation, and difficulty crossing the blood-brain barrier [9]. However, till now, there are no effective treatments available that can alter the main symptoms of autism or which can improve the cognitive and deficit symptoms of schizophrenia; the majority of the people who have epilepsy, depression, brain injury, and post-traumatic stress disorder have acquired a few satisfaction from the current therapy available. The discovery of new effective medication for NDs has proven difficult compared to other diseases. Most pharmaceutical companies have shifted their interest from the field of neurology to other fields [10]. Chances of failure of clinical trial rate in the last stages are higher for a neurological and psychiatric disorders as compared to other diseases; due to the complex physiology of the brain, there are fewer animal models available that can effectively predict the safety and efficacy of the drug for the disorder that mainly affects the cerebral cortex [11]. Drug discovery is a costly and risky process, while drugs used to treat neurological or psychiatric disorders not

only require a longer time to complete all stages of a clinical trial but also take much longer to complete the process of approval from a regulatory authority. The higher risk and high expenditure related to drug discovery and the development of neurological disorders are directly linked to scientific challenges. Several obstacles faced by pharmaceutical companies faces in discovering new drugs include: (a) Slow process of target identification and validation, (b) lack of appropriate animal models, (c) long duration of clinical trials paucity of knowledge regarding the disease's etiology [12]. One of the biggest hurdles in the establishment of the treatment of CNS disorder is because of the blood-brain barrier [13]. BBB restricts the permeation of therapeutic drugs to reach to the target site in the CNS therefore more than 98% of small molecular drugs remain ineffective in treating the CNS disorder [14].

Transportation of drugs through the BBB is a complex process requiring very sophisticated and nanosized particles. As nanoparticles have the potential to deliver drugs in various diseases, selenium nanoparticles (SeNPs) have been found to play a significant role in neurodegenerative diseases [15]. Various studies revealed that selenium nanoparticles have better bioavailability, improved antioxidant properties, and less toxicity than selenium-containing compounds. Thus selenium nanoparticles have free radical scavenging properties and improve behavior abnormalities and neurochemical alterations. Therefore, selenium nanoparticles have the potential to improve the impairment of memory and can be used as a potential therapy for NDs [16]. This book chapter provides a thorough overview of recent discoveries in the fields of investigation and use of nanoformulations for treating NCDs such as Parkinson's, Alzheimer's, ALS, and Huntington's, as well as the use of SeNPs for diagnosis and treatment.

2. Selenium nanoparticles in the management of CNS disorders

Due to the BBB and BCSFB, which prevents drug transport, treating ailments of the CNS is notoriously problematic. A promising clinical methodology for the intervention of some common NDs like, frontotemporal dementia, ALS, PD, and HD is provided by nanotechnology-based drug delivery methods, one of the new tactics to get around these obstacles and delivering medications to the CNS [17]. SeNPs could be a novel approach for treating such CNS disorders. Nanotechnology has emerged as an intriguing and promising new tool for treating NDs with considerable potential to solve issues with conventional methods. Nanostructured materials could traverse the BBB, target specific cells or signaling pathways, react to endogenous stimuli, transport genes, help axonal regeneration, and promote cell viability, among other specialized activities [18].

2.1 Role of SeNPs in treating CNS diseases

On the brain and neurons, selenium exhibits a direct antioxidant impact [19]. Low or moderate doses of selenium suppress cancer progression and have therapeutic benefits on NDs, including AD. Elevated levels of selenium increase the development of cancer cells and exhibit neurotoxicity. In *in vivo* and *in vitro*, selenium's antioxidant and anti-inflammatory activities have been established [20]. Selenium is a co-factor in the enzyme glutathione peroxidase, a scavenger. The catalytic properties of GSH-Px cause hydrogen peroxide (H_2O_2) to be transformed into water [19, 21–23]. A growing body of research shows that memory loss in AD patients is directly related to selenium deficiency in serum and hair samples. In animal studies and AD patients, selenium

supplementation has reportedly been shown to reduce the likelihood of cognitive issues [20, 24–27]. The exploration of selenium and selenoproteins in neurological disorders, such as AD, has attracted much interest. Proteins known as selenoproteins include selenium as the amino acid selenocysteine. Since antioxidant mechanisms are crucial for delaying the emergence and spread of AD, these are primarily expressed in human brain tissue [28].

Additionally, certain recently developed selenoproteins and SeNPs with exceptional physiological characteristics exist. These particles may replace traditional therapeutic medications in managing AD because of their great efficiency and low toxic effect [20, 29]. SeNPs may be a promising therapeutic molecule for treating AD, according to the Nazrolu et al. report [20]. Using the whole-cell patch clamp method, Yuan et al. investigated the effects of SeNPs on sodium influxes and the excitation of DRG (dorsal root ganglion) neurons [30]. According to their study, SeNPs appeared to reduce sodium influx in a concentration and time-dependent way, raising the possibility that SeNPs may be neurotoxic [20, 31, 32]. Epigenetic, chronic stress, metabolic, and dietary factors all have a role in developing HD, an untreatable condition that causes a gradual loss of brain functionality. According to studies, selenium (Se) concentration in the brain are inadequate for HD illness, but restoring Se regulation there may lessen neuronal death and functioning. Most research showed that nano-Se reduced peroxidation, prevented huntingtin protein aggregation, and suppressed the production of histone deacetylase family members at the mRNA level. Nano-Se offers great promise as a treatment for HD. Therapy for HD disease will derive from nano-Se NPs' ability to heal neuronal processes and shield against degradation under stress [33]. Recent research has crucially demonstrated Se's beneficial impact on HD. For instance, sodium selenite may reduce mutant huntingtin clumping and rates of oxidized glutathione in HD mouse brains [34]. SeNPs were reported to offer neuroprotection by upregulating Nrf2 and HO-1, suppressing the inflammatory process, and apoptotic pathway, and avoiding the emergence of oxidative stress. Upon the onset of epileptic seizures, SeNPs can counteract alterations in the concentration and functionality of neuromodulators. SeNPs have strong antioxidant, anti-inflammatory, and neuromodulatory properties that make them a potential candidate for use as an anticonvulsant medication [35].

Selenium has been investigated as a screening tool for several neurological disorders, including epilepsy, AD, and PD. Se is available in high levels in the grey matter areas and the glandular sections of the brain. It participates in several neurotransmission and dopaminergic pathways [36, 37]. A few elements identified as potential influences for the involvement of Se in Alzheimer's pathogenicity include its antioxidant, neuroprotective effects, influence on the regulation of cytoskeletal elements assembly, affinity for several neurotoxic metals, and competence to mitigate Aβ accumulation and tau proteins hyperphosphorylation [34, 36, 38]. Se has been worn to prevent dopaminergic neurons by many selenoproteins, supporting its ability to fend off PD. Se levels were also linked to aggressive behaviour, anxiety, and mood swings. Se application in neurological diseases may be beneficial for individuals with profound Se insufficiency and/or mutants in genes related to Se transport or selenoproteins synthesis. At the same time, brain Se levels are usually low, and high Se levels might be detrimental (**Figure 1**) [39, 40].

SeNPs have shown great potential in managing various CNS disorders through particular mechanisms. The cellular signaling pathways that regulate the metabolic activity of neurons (TSC1/TSC2, p-mTOR, mTORC1), antioxidant (FoxO1, β-catenin/Wnt, Yap1), and inflammatory system (jak2/stat3, Adamts-1),

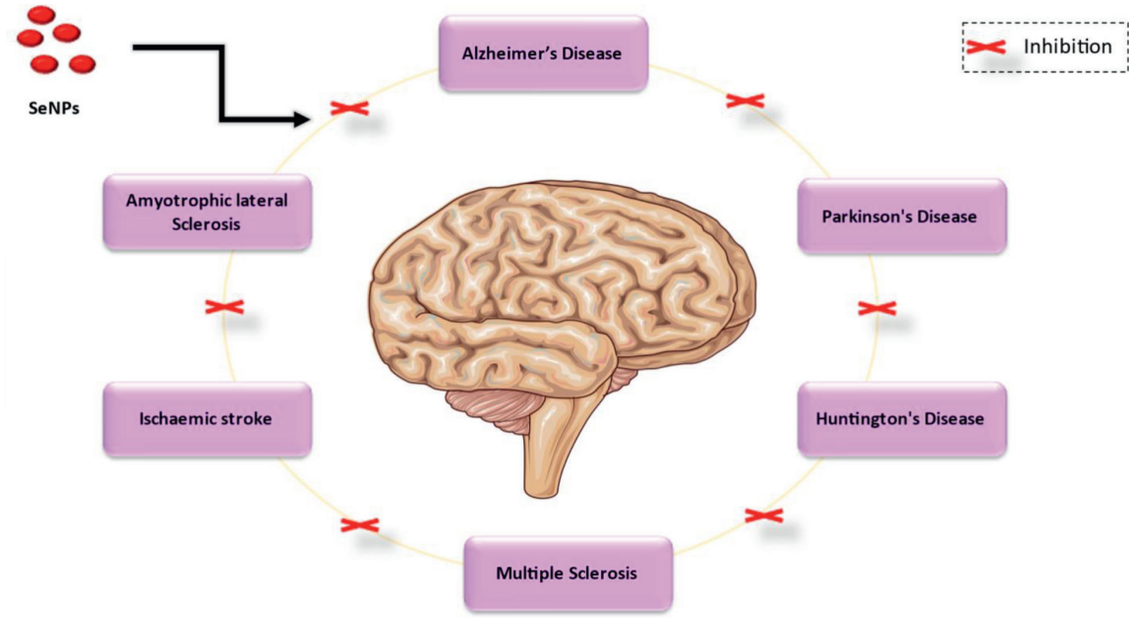


Figure 1.
Selenium nanoparticles in the management of several neurodegenerative diseases.

autophagy and induction of apoptosis (Mst1, ULK1, Bax, Caspase-3, and Bcl-2), and the preservation of hippocampal neurons (rictor/mTORC2) [41] these are the molecular mechanisms related with the neuroprotective activity of SeNPs. MST1 regulates neuronal cell death via Casp3 Signaling Pathway [42]. The JAK-STAT pathway prevents apoptosis in neurons. STAT3 is upregulated and stimulated selectively in regenerated neurons after axon damage. This pathway plays a direct role in forming glial scar tissue across lesions and neuronal restoration. After a CNS injury, STAT3 stimulation is required for the production of glial scars and the control of the spread of inflammation, both of which are essential for astrogliosis [43]. Numerous investigations have functionalized SeNPs with particular molecules, like sialic acid and epigallocatechin-3-gallate, to improve their penetrability toward the BBB. SeNPs are shown to minimize accumulation and stimulate their fragmentation to act as an antioxidant in the brain, either effectively or as part of GPx [20, 44] (**Figure 2**). Additionally, SeNPs were investigated in conjunction with substances that have demonstrated anti-disease Alzheimer's effects, such as resveratrol (Res) [45], curcumin (Cur) [46], chiral D-penicillamine (DPen) [47], and chlorogenic acid (CGA) [36, 48].

2.2 Types of SeNPs in the treatment of CNS disorders

SeNPs in conjugation with several molecules acts as an antioxidant and neuroprotective agent and has also been reported for various neurological diseases. Resveratrol's antioxidant and neuroprotective abilities, which counteract Aβ-aggregation and its oxidative consequences, have shown promise in the defense against AD. It has been demonstrated that Res-SeNPs selectively attach to Aβ through N-donors found in amino acids, forming a Se-N bond and enhancing Ressuppression on Cu^{2+}-induced Aβ aggregation. Res-SeNPs are non-toxic to neuroblastic cells (PC12 cells) and protect them against oxidative stress by reducing the apoptosis caused by Aβ, suggesting a potential synergism between SNPs and Res [45]. Curcumin also has demonstrated potential synergy with SeNPs in the therapy of AD. The antioxidant,

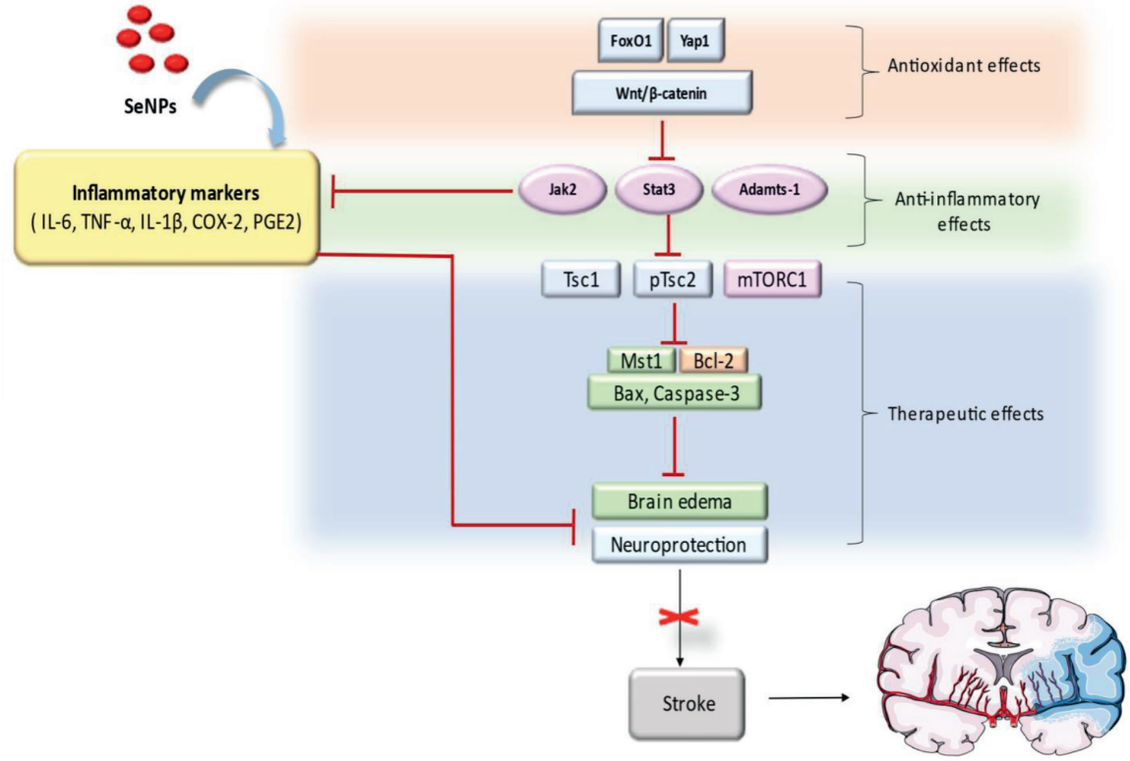


Figure 2.
Anti-inflammatory mechanism of SeNPs in management of central nervous system related diseases.

anti-Aβ inflammation and anti-Tau hyperphosphorylation capabilities of these NPs allowed them to pass through the BBB and bind to Aβ. It has been demonstrated that curcumin binds Aβ by hydrophobic contacts at the nonpolar regions of Aβ, enhancing their anti-inflammatory and antioxidant activities alongside Se [46]. As a result of their ability to bind to the N-donors of Aβ-proteins and form a Se-N bond, which prevents Aβ from aggregating them, CGA-SeNPs were shown to minimize Aβ-generated ROS in a dose-dependent manner, hindering their neurotoxicity and, consequently, lowering the rate of apoptosis. This was transcribed into a synergistic effect among CGA and SeNPs [49]. When given to transgenic mice 5XFAD with the mutation, the curcumin-loaded selenium-PLGA nanospheres developed by Huo et al. demonstrated a reduction in Aβ plaque production and inflammation [46]. Using an anti-Tfr receptor monoclonal antibody (OX26) as a functionalizing agent, PEG-SeNPs were also applied to treat stroke. OX26-PEG-SeNPs have been shown to play a function in preventing stroke in neuronal cells by minimizing the cellular edema brought on by aberrant Na^+ ion influx. When the middle cerebral artery was blocked in Wistar rats, SeNPs could reduces the infarction volumes, reduce the number of necrotic cells, increase the myelinated areas, and prevent the loss of axons in the hippocampal region [41]. SeNPs have also demonstrated promise in the battle against Huntington's disease. In HA759 mutant nematodes, SeNPs, in a dose-dependent manner, lowered neuronal death by reducing protein aggregates associated with HTT genetic variants and ROS, suppressing histone deacetylase mRNA, axonal degeneration, and improving reflexes [50]. Work on selenium-doped carbon quantum dots (Se-CQDs) has demonstrated their capacity to reduce ROS, and they have been successfully used to reduce secondary damage in TSCI. The findings showed that Se-CQDs had bioactivity and had a notable preventive role on astrocytes and PC12 cells toward H_2O_2-induced oxidative stress [51].

A frequent neurological condition called cerebral ischemia sets off a series of pathophysiological processes that include a drop in glucose and oxygen levels, an uncontrolled emission of glutamate, a fast rise in cellular calcium levels, and the production of free radicals. These occurrences consequently cause the endoplasmic reticulum and mitochondria's functions to be disrupted, which in turn causes the death of brain cells through apoptosis or necrosis [41, 52–54]. SeNPscan cross the BBB, builds up in the brain, and stops cell death from occurring. SeNPs are known to promote the production of BDNF and lower levels of Aβ and IL-6 in the hippocampus. Increased BDNF production reduces oxidative stress and prevents the degeneration of GABAergic neurons, particularly vulnerable to hypoxia and ischemia [55–57]. The mechanisms of the protective role of a modest dose of SeNPs on brain cells during OGD/R were examined by Turovsky et al. [58]. Additionally, the Bcl-2 family of proteins, the mechanisms of calcium homeostasis repair, suppression of mitochondrial and ER stress mechanisms, and eventually silencing of caspase-3 and inhibition of apoptosis are all part of SeNPs protective measure [58, 59].

Fei Gao et al. created selenium-chondroitin sulfate nanoparticles (CS@Se) as part of a multitargeted therapy for AD. Amyloid-ß (Aß) accumulation was successfully prevented by CS@Se, and SH-SY5Y cells were shielded against cytotoxicity brought on by $Aß_{1–42}$. In SH-SY5Y cells, okadaic acid-induced actin cytoskeleton disruption was dramatically reduced by CS@Se. The ROS and MDA levels were reduced by CS@Se, while the amounts of GSH-Px were elevated. This research shows that CS@Se might reduce tau protein hyperphosphorylation, ameliorate oxidative stress, prevent Aß from aggregating, and lessen cytoskeleton disruption. CS@Se is an effective multifunctional drug for the management of AD [60]. Xian Guo developed SeQDs, which have a multitarget therapeutic impact and can easily enter the BBB, to improve the therapeutic effect of pharmaceuticals through the BBB. SeQDs' unique fluorescence properties could be used to diagnose and manage AD. SeQDs are highly effective at scavenging free radicals and shielding cells from oxidative stress. By down-regulating PHF1 and CP13, the SeQDs can dramatically reduce tau protein phosphorylation and further neutralize free radicals, rebuild metabolic activity, preserve nerve cell solidity, and defend nerve cells from oxidative damage. These effects preclude Aß-mediated cytotoxicity and Aß aggregation, preventing the AD cascade reaction. Compared to conventional single-target medications, usingSeQDs in AD therapy has many benefits and offers a fresh approach to the co-managementof neurological illnesses [61]. The mechanism of SeNPs is depicted in **Figure 3**.

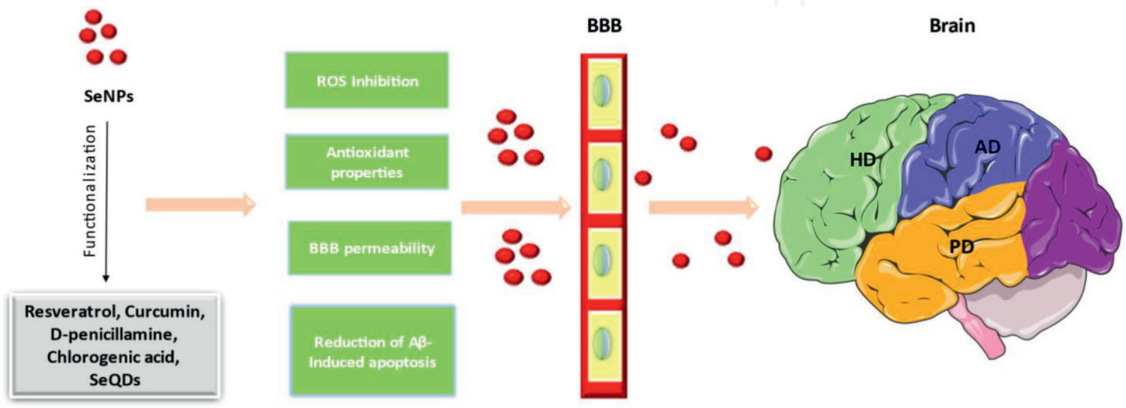


Figure 3.
SeNPs against various neurodegenerative disorders.

3. Therapeutic application of selenium nanoparticles in CNS disorder

3.1 Alzheimer's disease

AD is a progressive neurodegenerative disease; the pathological hallmark of this disease is the deposition of Aβ plaques. Various attempts have been made to develop therapies that potentially inhibit its deposition in the brain; in this regard, nanoparticles have shown promising results due to their distinctive physiochemical properties of small size and large surface area. Se is one of the most important mineral nutrients having a wide range of pharmacological actions. Studies have found that selenium has a neuroprotective effect. Due to the high stability of SeNPs, it has potential effects on the neurotoxicity of $A\beta_{42}$ in primary cultures of murine hippocampal neurons [62]. In human clinical trials, curcumin has been found as a highly efficacious compound without exerting any adverse effect, even when taken at a higher dose of 4 g/day. Curcumin forms intermolecular hydrogen bonds and binds effectively with Aβ plaques in AD. In AD, curcumin's drug delivery properties were modified by encapsulating SeNPs and changing the surface of the poly-lactide-co-glycolide (PLGA). In preclinical studies of memory impairment in mice models, it was found that the drug delivery system of curcumin-loaded SeNPs has the potential to decrease the aggregation of Aβ plaque in Alzheimer's disease mice model [46]. Moreover, selenium-chondroitin sulfate nanoparticles were also found to decrease the aggregation of amyloid-β and reduce the tau protein hyperphosphorylation by targeting the GSK-3β [63]. Another research revealed that chitosan-coated SeNPs (ChSeNPs) could enhance the effectiveness of stem cell-based therapy to attenuate the neurotoxicity in the streptozotocin-induced model in rats [64].

3.2 Parkinson's disease

PD is the second most prevalent CNS disorder after AD. Oxidative stress is considered one of the major factors responsible for this disease, causing neuronal death and apoptosis. Therefore, behavioral abnormalities in PD can be improved by decreasing the level of oxidative stress. As selenium possesses antioxidant properties, in preclinical studies, the neuroprotective effect of glycine-nano-selenium on oxidative stress was evaluated in PD rat model, and oxidative stress is induced by using 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) in the rat. It was found that oxidative stress in PD rat model was reduced by administering intragastric glycine nano-selenium, which ultimately reduced the neurobehavioural abnormalities in rats [65]. The administration of selenium in humans and animals has shown a rise in the level of glutathione and glutathione peroxidase, thus slowing the degeneration of neurons and preventing the depletion of dopamine levels. Hence it is regarded as an important micronutrients in Parkinson's disease as well [66].

3.3 Huntington's disease

Various studies have also been conducted for Huntington's disease by using selenium nanoparticles. HD is an inherited autosomal dominant disease caused by repeated trinucleotide sequence CAG that encodes for huntingtin protein [67]. Various laboratory findings suggest that oxidative stress is a major factor in Huntington's disease's pathogenesis. But due to poor knowledge of particular oxidative biomarkers, no antioxidants have effectively prevented neurodegeneration

in Huntington's disease [68]. Studies have found Se to play a protective role in Huntington's disease, such as sodium selenite has the potential to lower mutant huntingtin aggregation and oxidized glutathione levels in the brain of HD mice model [34]. Recent studies have found a low level of Se in the brain of HD patients. Attenuating neuronal dysfunction can be achieved by maintaining the level of Se in the brain. In a preclinical study of HD models, Selenium nanoparticles have been found to prevent neuronal loss and improve behavioral dysfunction. Molecular testing has shown that selenium nanoparticles also prevent the damage produced by oxidative stress and attenuate the aggregation of huntingtin proteins. Thus Selenium nanoparticles are an effective therapy for Huntington's disease [50].

3.4 Amyotrophic lateral sclerosis

ALS is a chronic, deadly and irreparable NDs which involves the degradation of motor neurons in the motor cortex, brainstem, and spinal cord, which results in paralysis and death due to respiratory failure [69]. Because of the absence of efficient treatment, the majority of patients pass away within 3–5 years of assessment. Several cases of ALS are sporadic, while 15% of the cases are familial [70]. Genetic defects in SOD1 were found to be the first causative mutation involved in the pathology of ALS [71]. Apart from this, more than 50 genes were reported to be involved in ALS. The most common ones include mutations in chromosome 9 open reading frame 72 (*C9orf72*), TAR DNA-Binding (*TARDBP*), and fused in sarcoma (*FUS*) [72]. Recently in vitro studies have shown organo-selenium compound to potentially protect the neuronal damage and thus can be used as an alternative therapy in ALS [73].

3.5 Epilepsy

Selenium nanoparticles can also be used in other CNS disorders such as epilepsy. SeNP also has potential anticonvulsant activity due to its extensive antioxidant, anti-inflammatory, and neuromodulatory effect. Administration of SeNP decreases the duration of tonic, myoclonic and generalized seizures and can be used as an effective therapy in epilepsy [35]. SeNP can effectively cross the BBB and thus can be used to enhance the delivery of anti-cancer drugs in the brain, such as in the case of glioma in humans [74]. Drug delivery to cross the BBB is a complex process, and it requires a nanosized particle so that the drug can reach the brain. In this regard, SeNPs plays a vital role in the management of NDs (**Table 1**).

4. Mechanism of SeNPs in neurodegenerative disease

Selenium, a crucial trace element in both man and livestock, is essential in managing the biological stability of the brain and possesses neuroprotective properties. Various selenoproteins were also found to be involved in controlling NDs [80]. SeNPs significance in NDs has been widely reported in recent years (**Figure 4**), considering that neurons are highly vulnerable to damage from oxidative stress-related injury for variety of reasons, including excessive oxygen utilization (about 25% of the total body utilization). There is a substantial quantity of polyunsaturated fatty acids and low amount of antioxidant enzymes [81]. Natural antioxidants are frequently utilized to treat neurological illnesses since oxidative stress is one of the primary contributors to their etiology. Yet, they are ineffective [80], and as a result, using

Disease	SeNPs	Animal model	Mechanism	Outcome	Reference
Alzheimer' disease	Cur/Se-PLGA nanospheres	The transgenic 5XFAD mice	Inhibited Aβ aggregation	Effective for AD treatment and to provide delivery at the site of target	[46]
	B6-SA-SeNPs	PC12 cells andbEnd.3 cells	B6-SA-SeNPs prevent the deposition of Aβ and effectively cross the BBB	B6-SA-SeNPs can be used to treat AD and have antioxidant and antiamyloid properties	[75]
	Selenium-chondroitin sulfate nanoparticles (CS@ Se)	SH-SY5Y cells	Prevent Aβ from clumping together, lessen cytoskeleton deterioration, combat oxidative stress, and lessen tau protein hyperphosphorylation	Potent multifunctional agent for AD	[63]
	Chitosan-coated Selenium nanoparticles (ChSeNPs)	Streptozotocin induced neurotoxicity in a rat model of AD	Decreases the neurotoxicity by increasing the antioxidant capacity	Decrease Aβ deposition and attenuate memory impairment	[64]
	SeNPs	Streptozotocin-induced neurotoxicity in the male rat of AD	SeNPs help in survival of neurons by regulating the system of oxidative stress, Cellular metabolite, and inflammatory reactions and maintaining the functional properties of the hippocampal neurons	SeNPs improve cognition by increasing the brain's antioxidant capacity, which inhibits Aβ aggregation pathways	[16]
	The combined therapy of SeNPs and stem cells	STZ-induced AD model	By lowering the accumulation of Aβ and raising the level of BDNF	SeNPs improve stem-cell-based therapy's ability to lessen cognitive deficits	[76]
Epilepsy	SeNPs	Pentylenetetrazole (PTZ)-mediated epileptic seizuresin mice	By inhibiting the apoptosis, oxidative stress and inflammatory response	Supplementation of SeNPs delays the onset and decreases the duration of tonic, myoclonic and generalized seizures	[35]
Parkinson's Disease	Glycine nano-selenium	MPTP induced neuronal abnormalities in a PD rat model	Decreased oxidative stress reduces neurocognitive disorders in rat brain	Improves behavior abnormalities and prevents the loss of dopaminergic neurons	[65]
Huntington's disease	Selenium nanoparticles	Transgenic HD models of *Caenorhabditis elegans*	SeNPs act by attenuating oxidative stress and inhibiting the aggregation of huntingtin proteins	Prevent neuronal damage and improves behavioral dysfunction	[50]

Disease	SeNPs	Animal model	Mechanism	Outcome	Reference
Amyotrophic Lateral Sclerosis	Selenium nanoparticle	—	Act by reducing oxidative stress	Inhibit amyloid-like aggregation of SOD1 in familial ALS	[77]
Spinal Cord Injury	TSIIA@SeNPs-APS	PC12 cells	Inhibited excessive ROS and reduced cell apoptosis	Potential therapeutic effects in the anti-oxidation therapy of SCI	[78]
	SeNPs@GM1/TMP	PC12 cells	Inhibiting excessive ROS and reducing cell apoptosis	Provide neuroprotective effect	[79]

Table 1.
Selenium nanoparticles showing promising results in neurodegenerative disease.

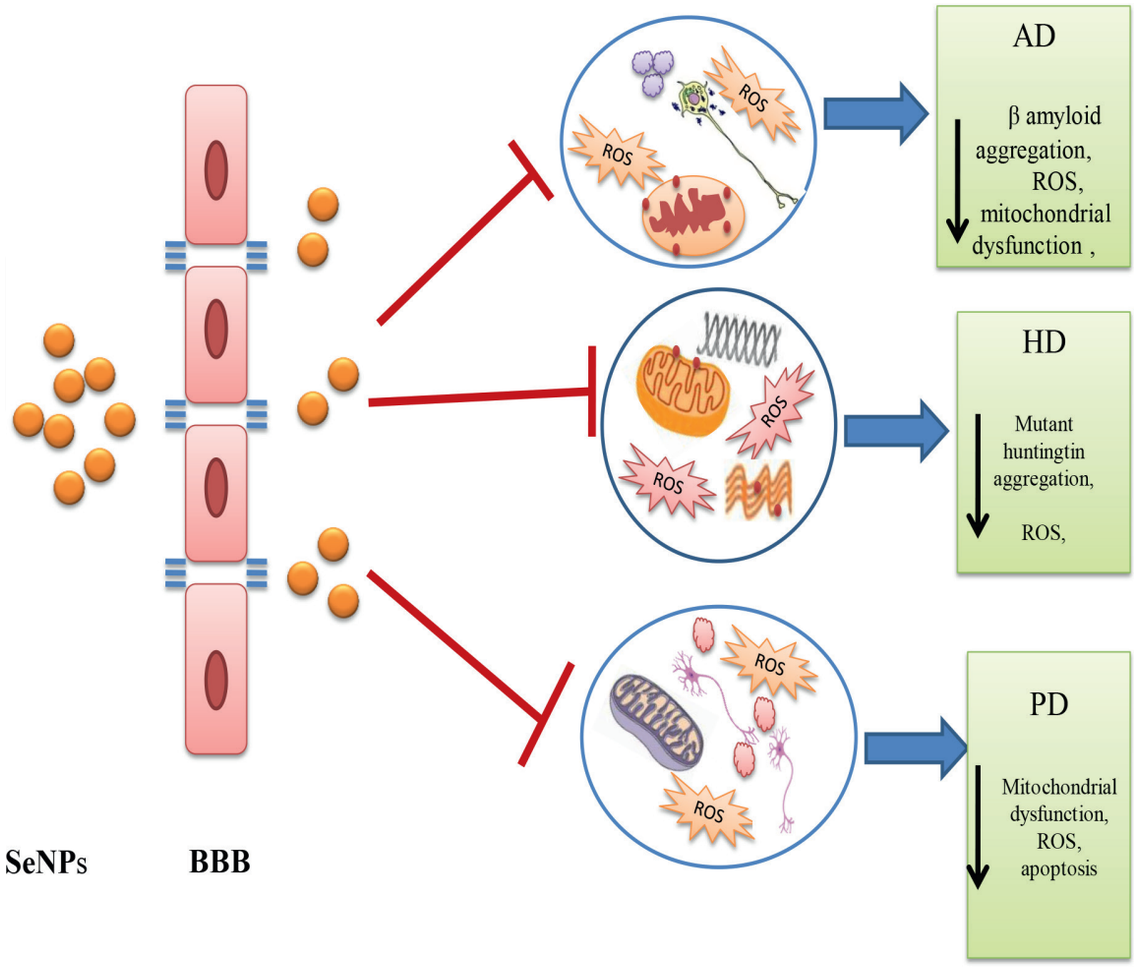


Figure 4.
Schematic representation of the mechanism of SeNPs in neurodegenerative disease.

antioxidants in the form of nanoparticles is growing in popularity. Se's capacity to pass the BBB and suppress Aβ aggregation are two of its key effects in AD [82]. Se was found to have a beneficial impact on the activity of H_2O_2absorption, the generation of intracellular ROS, and the aggregation of Aβ, which is found in the investigation of Se-containing clioquinol derivatives during the oxidation of Aβ caused by Cu^{2+} [83]. It is well recognized that the formation of improperly folded proteins in the brain and their aggregation is one of the primary causes of neurodegenerative disorders. Since Aβ may acquire several formats in AD, amyloid plaques are recognized due to improper protein folding and aggregation in the brain. According to studies, metal ions like Cu^{2+}, Zn^{2+}, and Fe^{2+} can bind to Aβ and co-localize with amyloid plaques in exceptionally high concentrations [84]. As a result, the use of metal chelators, like clioquinol (CQ), for AD treatment is of great interest. However, most chelators can also bind to other metal-containing proteins, which is undesirable and might disturb normal physiological functioning in the body [85].

SeNP has been shown to attach to Aβ, influence metal ions, and change their surfaces, such as ligands, charges, or reactivity [86]. As a result, it was demonstrated that l-Cys-modified SeNP (Cys-SeNP) could prevent $Aβ_{40}$ fibril formation caused by Zn^{2+} [87]. A multifunctional therapy for AD treatment has also been developed using chondroitin selenium sulfate (CS@Se) nanoparticles [63]. Chondroitin sulfate is a sulfated glycosaminoglycan (GAG) that binds to the protein core to generate the proteoglycan chondroitin sulfate (CSPG). The primary constituent of Perineuronal networks is

CSPG [88]. $A\beta_{1-42}$ induced cytotoxicity in SH-SY5Y cells (human neuroblastoma) was prevented by CS@Se, which demonstrates its ability to prevent amyloid-β aggregation efficiently. Additionally, CS@Se lowered the hyperphosphorylation of tau (Ser396/Ser404), reduced the levels of ROS and MDA, and enhanced the levels of GSH-Px [63].

In HD, a hereditary neurodegenerative condition that results in the loss of brain cells and is linked to motor, cognitive, and behavioral impairments in adult patients, recent investigations have shown that Se has a protective function. Variable CAG trinucleotide repeats, found in the transcript that codes for the HTT, are a feature of this autosomal dominant disorder. The DNA repair system and mitochondrial malfunctions can be harmed by cumulative oxidative stress, which is thought to play a significant role in HD and other NDs. It has been demonstrated that sodium selenite can lessen mutant huntingtin aggregation and oxidize glutathione levels in HD mouse brains [34]. There is no viable treatment to stop HD from progressing or cure it. SeNP has been demonstrated to protect *C. elegans* from oxidative stress, ameliorate behavioral dysfunction, and prevent neuronal death at doses below 2 μM [50]. Nanoparticle therapy reduced the quantity of ROS, demonstrating their antioxidant properties, and stopped mutant HTT from aggregating in vivo.

After AD, PD is the second progressive neurological illness. The pathophysiology of PD is still unknown, although studies have revealed that oxidative stress, which causes neuronal death and apoptosis, is a key pathogenic component of PD [89]. An established neurotoxin called MPTP is used as a model for PD research. It has been demonstrated that MPTP can cause PD by boosting oxidative stress, which causes dopamine neurons to degenerate and causes neurobehavioral problems. By raising SOD and GSH-PX activity and lowering MDA levels, glycine-SeNP had an anti-oxidative effect on neurons. As a result, glycine-SeNP has the potential to treat Parkinson's disease [65]. Behavioral, molecular, and neurochemical alterations are the hallmarks of the persistent neurological condition known as epilepsy. Epilepsy is a neurological condition that affects between 0.5% and 1% of the world's population and is characterized by repeated, spontaneous seizures. Numerous conditions, such as cerebrovascular diseases, trauma, cancer, oxygen deprivation, infections, and genetic problems in brain development, can contribute to the development of seizures [90]. SeNP is a promising epilepsy treatment because of its excellent BBB-crossing capacity and few side effects. The malfunction of the mitochondria and endoplasmic reticulum causes oxidative stress, which increases the formation of free radicals and depletes neuronal antioxidant molecules. Oxidative stress is linked to both neuronal hyperexcitability and epileptogenesis [91]. The structure of selenoproteins and selenoenzymes include Se, which can inhibit ROS and, consequently, the onset of oxidative damage. Additionally, SeNP help to restore the levels of the neurotransmitters ACh, NE, DA, 5-HT, and GABA in brain tissue, which helps to restore neuronal connections and reduce apoptosis [35].

5. Diagnostic applications of SeNPs in CNS disorders

One of the main obstacles in treating and diagnosing CNS diseases is the inability of therapeutics to cross the BBB. A more comprehensive and accurate nanoparticle design is required to deliver therapeutic and diagnostic compounds to the CNS95 effectively. The evaluation and management of neurological conditions such as AD, PD, HD, head injuries, brain tumors, and epilepsy remain difficult tasks at this time. Numerous prospective medications have been studied to treat various neurological illnesses, but their efficacy is still constrained due to various difficulties [18].

For biomedical applications such as medication administration, bioimaging, and biosensing in CNS illnesses, a variety of inorganic NPs provide considerable efficiencies [92]. SeNPs offer a wide range of applications, including assessing and treating health-related problems that would otherwise be impossible to identify or address. Khalid et al. have examined the intrinsic fluorescence of SeNPs and their diagnostic potential. They discovered SeNPs' inherent fluorescence and its usefulness for nanoscale monitoring of cellular mechanisms. SeNPs' photoluminescence spectrum ranges from the visible to the near-infrared, making it useful for neuroblastoma cell tracking and their in vitro imaging. SeNPs have also been investigated as a peroxide biosensor. For accurate H_2O_2 sensing, Wang et al. produced semiconductor monoclinic SeNPs and they can be used to diagnose and assess the state of oxidative stress [93]. To produce an H_2O_2 sensor, plant-based rod-shaped SeNPs were created utilizing lemon fruit extract as a reducer and capping agent. Hydrogen peroxide sensing is a crucial component since it initiates a variety of cellular processes [94]. As selenium levels are said to be low in patients, SeNPs could be utilized to diagnose AD and HD.

Further research can be done on diagnostic techniques for detecting GPx or selenium levels. By focusing on many physiological pathways that control the metabolic status, inflammatory responses, oxidative defense system, and apoptosis, SeNPs functionalized with monoclonal antibodies (OX26) may be capable of defending against ischemic stroke [95]. The nano-based technique has significance for multiple sclerosis diagnosis and its involvement in treatments. The very sensitive DNA-carrier gold NPs-based coding technique can identify biomarkers in CSF or damaged brain tissue. This diagnostic test may be very helpful in diagnosing MS because radio imaging is the standard gold method for MS assessment (**Figure 5** and **Table 2**) [18].

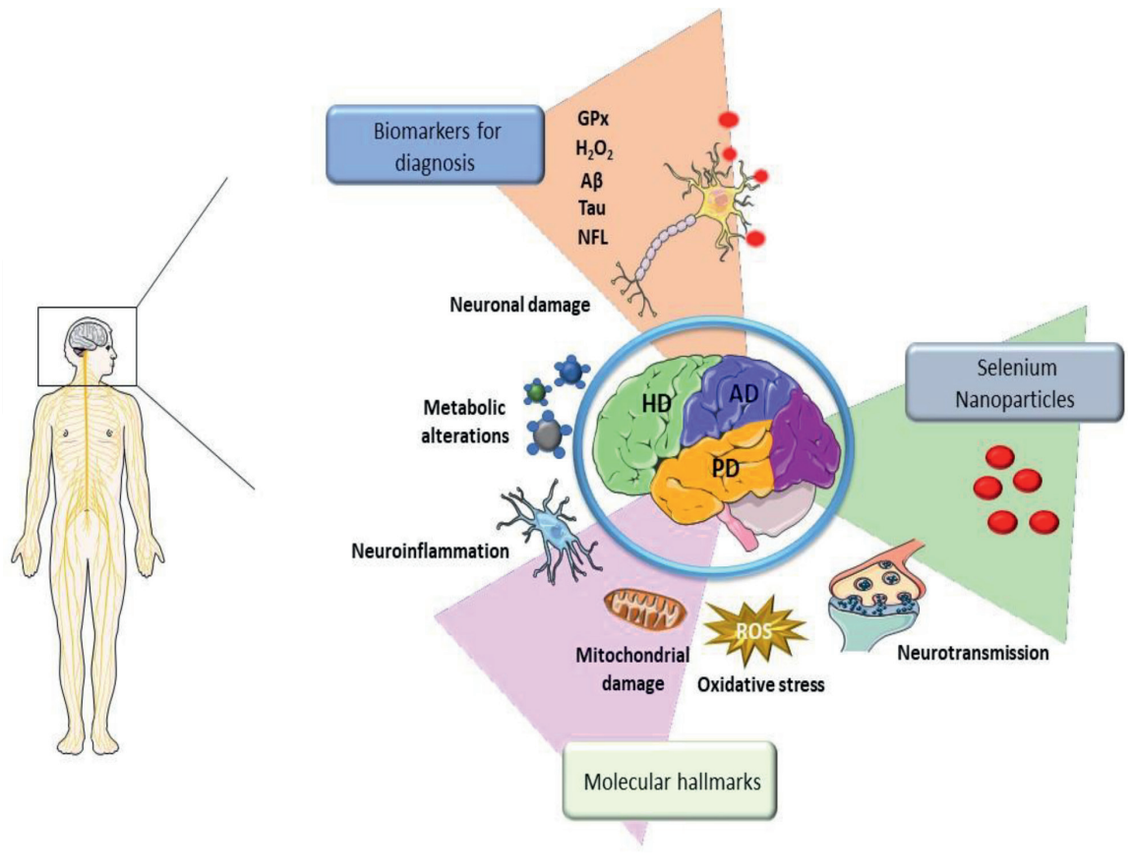


Figure 5.
Mechanism of selenium nanoparticles in the diagnosis of neurodegenerative disorders.

CNS disorder	SeNPs	Animal model	Outcome/inference	Reference
Brain diseases	Semiconductor monoclinic SeNPs	Mouse model	Useful for neuroblastoma cell tracking and in vitro imaging	[93]
	$Cu_{2-x}Se$ nanoparticles	Living mouse	Facilitated photothermal and single-photon emission computed tomography imaging tracking the restoration of the ruptured BBB by using ultrasound to infiltrate the brain	[96]
	Biogenicselenium nanorods	—	H_2O_2 sensor is developed, showing biomedical cellular peroxide sensing with low limits through the naked eye	[94]
Stroke	SeNPs functionalized with OX26	Murine model	For detecting GPx levels and being capable of defending against ischemic stroke	[95]
	OX26-PEG-Se NPs	Murine model	Using the crucially important for inflammation mTOR metabolic controller and associated signaling pathways such hippo, ERK5, Tsc1/Tsc2 complex, FoxO1, wnt/β- catenine signaling pathway, jak2/stat3 signaling pathways, and Adamts1	[41]
AD	State-of-the-art nanoparticles	Mouse model	Due to their efficacy as diagnostic tools, proteins like NFL, MMPs, p-tau217, and BACE are among the most potential biomarkers	[97]
	Selenium functionalized with Chondroitin sulfate	SH-SY5Y cells	Decreased the levels of ROSand MDA, increased the levelsof GSH-Px, and attenuatedthe hyperphosphorylation of tau by regulatingthe expression of GSK-3β	[63]

Table 2.
List of some selenium nanoparticles in the diagnosis of CNS diseases.

6. Future perspective

Nanotechnology-driven formulation techniques have enormous potential in the twenty-first century's drug research and discovery. Several nanotechnology-based preparations are available and can be easily accessible from the market, and this fact is not hidden from everyone. Se nanoparticles, an important trace element needed as a co-factor for various enzymes, have become an important tool in diagnostics and therapeutics for treating various illnesses, including neurodegenerative disorders. Indeed, the bulk of reported research has a significant SeNPs-based justification [98]. The development of nanotechnology has increased the number of possible therapeutic approaches to halt the course of AD. Oral/gastric barriers and the BBB are conventional neurotherapeutic obstacles that are effectively overcome by the proper design and production of NPs, improving the physicochemical characteristics of drugs in biological systems. However, the field of AD nano-therapeutics still has several limitations. There have been many in vitro experiments demonstrating the capability of SeNPs and its effectiveness, but there have been few in vivo trials. Therefore, future studies of these SeNPs may show systemic efficiency or toxicity in biological systems over the long run that can be contrasted to *in vitro* methods. Therefore, in the near future, potential, affordable AD treatments may result from evaluating the safety and efficacy of appropriate SeNPs in human clinical trials [99]. Recent research findings suggest that SeNPs can provide promising results in for the treating of HD

through diets. In the future, an in-depth knowledge is required to know the mechanism of nano-Se in preventing the HD and their connection between physicochemical features and therapeutic potential will be beneficial for treating HD disease.

Furthermore, compared to other selenium species, the rational design of nanoSe may enhance dosage tolerance for HD therapy in the future [50]. It is abundantly evident that the current situation demands immediate and effective treatment for neuroprotection, neurorestorative, and neuroregeneration. Clinical translation in neurodegenerative disorders has become more challenging due to the lack of appropriate biomarkers, delayed diagnosis, incomplete understanding of molecular pathogeneses, lack of useful disease models, insufficient clinical protocol, and the generally asymptomatic nature of the disease. The deficiency of proper animal models that accurately reflect some crucial characteristics of ND in humans and a shortage of samples of patients are the two key limitations to therapeutic advancement. Therefore, the successful development of effective human disease-modifying medicines can be achieved through representative animal models.

Furthermore, inadequate knowledge of the molecular rationalization of aging and its biological impact and clinical consequences of neurodegenerative disorder contributes to delayed progress in translation. Success in therapeutic trials may result from shifting the focus from the primary pathogenic proteins to a plethora of disease-related proteins. In the future, using human CNS organoids to model neurological diseases is a realistic choice.3D brain organoids with the appropriate physicochemical signaling cues can be used to simulate patient-specific tissue patterns. Although organoids greatly improve the deep understanding of the development of brain and neurodegenerative illnesses, there are still several gaps in the field, including vascularization and non-neuronal cells. The targeting of particular brain cells in various NDs, such as in PD dopaminergic neurons are mainly targeted and this must be questioned when nanoformulation are prepared.

Additionally, it is important to consider adjusting pharmacokinetics and pharmacodynamics characteristics before administering NP [100]. Nanomedicine-based delivery systems raise concerns about their potential for toxicity, including the possibility of inflammation of neurons, excitotoxicity, mitochondrial and DNA damage, and some allergic reactions. Therefore, thoroughly researching the biocompatibility as well as biodegradability of nanodrugs is important [101]. The main function of the SeNPs in pharmacological defense against different types of inflammatory as well as oxidative stress-mediated situations is already discussed. However, nothing is known about how the SeNPs influence the pharmacokinetics and pharmacodynamics properties of selenoproteins. Most of the available research was not well structured and did not include comparisons to other Se sources. Future research should focus on understanding how selenoproteins contribute to the reported pharmacological effect and include relevant sources of Se [98].

7. Conclusion

Leading contributors to the world's disease burden are CNS illnesses, which encompass a wide range of brain diseases with both short- and long-term disabilities. Because of the shift in lifestyle and the swift, ongoing environmental degradation, CNS disorders like AD, PD, stroke, brain tumors, and neuroinflammation are distressingly damaging to humanity. With their complicated anatomy, specific microenvironment, and specificity to any foreign material such as drugs, BBB and BCSFB are the primary physiological barriers that pose a significant bottleneck for the effective

therapy of CNS disorders and brain tumors. This presents the greatest hurdle to CNS drug discovery. SeNPs may help with the current issue of the lack of multifaceted drugs for various CNS disorders, which may contribute to various distinct biological mechanisms. SeNPs have led to cutting-edge nanoscale targeting approaches among the different treatment approaches. They are at the forefront of a new paradigm that could administer active agents with intriguing dynamics to treat these disorders. SeNPs offer superior medicinal qualities to selenium salts and lesser toxicity, despite their narrow therapeutic window. The current demand for effective nano-based treatments is concentrated on neuroprotection and restoration, which would greatly benefit from other nano-based strategies and advancements in the anatomy, pathology, and physiology of neuronal cells. Several nanoscale treatments (SeNPs) were found to treat neurological illnesses in AD, PD, and stroke models, including the suppression of Aβ oligomerization, reduction of ROS, and enhancement of functioning neural networks (**Figure 5**). SeNPs have allowed it to administer chemotherapy and antisense gene therapy in malignant brain tumors with pinpoint accuracy. This has led to a striking reduction in disease development in both *in vitro* and *in vivo* research.

SeNPs could completely alter how we address CNS-targeted therapeutics because of their competency to be nanoengineered so that the drug or carrier can encounter the BBB, diffuse inside the brain, and target specific cells or signaling systems for therapeutic delivery. This opens up new paths in the intervention of neurological diseases and has an extremely great prospect. It is very conceivable that SeNPs will alter how CNS disorders are treated. Shortly, the real objective of drastically increasing survival rates will be accomplished.

Abbreviations

AD	Alzheimer's disease
ALS	amyotrophic lateral sclerosis
APP	amyloid protein precursor
BBB	blood-brain barrier
BCSFB	blood-cerebrospinal fluid barrier
BDNF	brain-derived neurotropic factor
CNS	central nervous system
CSF	cerebrospinal fluid
DRG	dorsal root ganglion
FoxO1	Forkhead box protein O1
GSH-Px	glutathione peroxidase
GSK-3β	glycogen synthase kinase-3 beta
HO-1	heme oxygenase-1
HTT	Huntingtin protein
MDA	Malondialdehyde
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
mTORC1	mammalian target of rapamycin complex 1
NDs	neurodegenerative diseases
Nrf2	nuclear factor erythroid 2-related factor 2
OGD/R	oxygen glucose deprivation/re-oxygenation
PD	Parkinson's disease
PLGA	poly-lactide-co-glycolide
p-mTOR	phosphorylated mammalian target of rapamycin

Se-CQDs	selenium-doped carbon quantum dots
SeNPs	selenium nanoparticles
SOD	superoxide dismutase
TSC	tuberous sclerosis
ULK1	Unc-51 like autophagy activating kinase1
WHO	World Health Organization
Wnt/ß-catenin	Wingless/Integrated ß-catenin
Yap1	Yes-associated protein 1

Author details

Jonaid Ahmad Malik[1], Jeba AjgarAnsari[2], Sakeel Ahmed[3], Archana Rani[4], Shabana Yasmeen Ansari[5] and Sirajudheen Anwar[6*]

1 Department of Biomedical Engineering, Indian Institute of Technology Ropar, Rupnagar, Punjab, India

2 Department of Pharmaceutics, Government College of Pharmacy, Aurangabad, Dr. Babasaheb Ambedkar Marathwada University, Maharashtra, India

3 Department of Pharmacology and Toxicology, National Institute of Pharmaceutical Education and Research, Ahmedabad, India

4 Department of Pharmaceutical sciences, Guru Nanak Dev University, Amritsar, India

5 Pharmaceutical Unit, Department of Electronics, Chemistry and Industrial Engineering, University of Messina, Messina, Italy

6 Department of Pharmacology and Toxicology, College of Pharmacy, University of Hail, Hail, Saudi Arabia

*Address all correspondence to: si.anwar@uoh.edu.sa

IntechOpen

References

[1] Jagaran K, Singh M. Nanomedicine for neurodegenerative disorders: Focus on Alzheimer's and Parkinson's diseases. International Journal of Molecular Sciences. 2021;**22**(16):9082. DOI: 10.3390/IJMS22169082

[2] Checkoway H, Lundin JI, Kelada SN. Neurodegenerative diseases. IARC Scientific Publications. 2011;**163**:407-419. DOI: 10.1071/rdv24n1ab251

[3] Tysnes OB, Storstein A. Epidemiology of Parkinson's disease. Journal of Neural Transmission. 2017;**124**(8):901-905. DOI: 10.1007/S00702-017-1686-Y

[4] Rocca WA. The burden of Parkinson's disease: A worldwide perspective. Lancet Neurology. 2018;**17**(11):928-929. DOI: 10.1016/S1474-4422(18)30355-7

[5] Talbott EO, Malek AM, Lacomis D. The epidemiology of amyotrophic lateral sclerosis. Handbook of Clinical Neurology. 2016;**138**:225-238. DOI: 10.1016/B978-0-12-802973-2.00013-6

[6] Hanif S, Muhammad P, Chesworth R, et al. Nanomedicine-based immunotherapy for central nervous system disorders. Acta Pharmacologica Sinica. 2020;**41**(7):936-953. DOI: 10.1038/s41401-020-0429-z

[7] Chapman CD, Frey WH, Craft S, et al. Intranasal treatment of central nervous system dysfunction in humans. Pharmaceutical Research. 2013;**30**(10):2475-2484. DOI: 10.1007/S11095-012-0915-1/FIGURES/1

[8] Durães F, Pinto M, Sousa E. Old drugs as new treatments for neurodegenerative diseases. Pharmaceuticals (Basel). 2018;**11**(2):44. DOI: 10.3390/PH11020044

[9] Di Paolo M, Papi L, Gori F, Turillazzi E. Natural products in neurodegenerative diseases: A great promise but an ethical challenge. International Journal of Molecular Sciences. 2019;**20**(20):5170. DOI: 10.3390/IJMS20205170

[10] Paul SM, Mytelka DS, Dunwiddie CT, et al. How to improve R&D productivity: The pharmaceutical industry's grand challenge. Nature Reviews. Drug Discovery. 2010;**9**(3):203-214. DOI: 10.1038/nrd3078

[11] Hyman SE. Revolution stalled. Science Translational Medicine. 2012;**4**:155. DOI: 10.1126/SCITRANSLMED.3003142

[12] Pankevich DE, Altevogt BM, Dunlop J, et al. Improving and accelerating drug development for nervous system disorders. Neuron. 2014;**84**(3):546-553. DOI: 10.1016/J.NEURON.2014.10.007

[13] Banks WA. From blood–brain barrier to blood–brain interface: new opportunities for CNS drug delivery. Nature Reviews Drug Discovery. 2016;**15**(4):275-292. DOI: 10.1038/nrd.2015.21

[14] Li G, Shao K, Umeshappa CS. Recent progress in blood-brain barrier transportation research. Brain Targeted Drug Delivery Systems: A Focus on Nanotechnology and Nanoparticulates. 2019:33-51. DOI: 10.1016/B978-0-12-814001-7.00003-2

[15] Rajeshkumar S, Ganesh L, Santhoshkumar J. Selenium nanoparticles as therapeutic agents in neurodegenerative diseases. Nanobiotechnology in Neurodegenerative Diseases. 2019:209-224. DOI: 10.1007/978-3-030-30930-5_8/COVER/

[16] Gholamigeravand B, Shahidi S, Amiri I, Samzadeh-kermani A, Abbasalipourkabir R, Soleimani AS. Administration of selenium nanoparticles reverses streptozotocin-induced neurotoxicity in the male rats. Metabolic Brain Disease. 2021;**36**(6):1259-1266. DOI: 10.1007/S11011-021-00713-8/FIGURES/7

[17] Nguyen TT, Dung Nguyen TT, Vo TK, et al. Nanotechnology-based drug delivery for central nervous system disorders. Biomedicine & Pharmacotherapy. 2021;**143**(July):112117. DOI: 10.1016/j.biopha.2021.112117

[18] Naqvi S, Panghal A, Flora SJS. Nanotechnology: A promising approach for delivery of neuroprotective drugs. Frontiers in Neuroscience. 2020;**14**(June):1-26. DOI: 10.3389/fnins.2020.00494

[19] Nazıroğlu M. Role of selenium on calcium signaling and oxidative stress-induced molecular pathways in epilepsy. Neurochemical Research. 2009;**34**(12):2181-2191. DOI: 10.1007/S11064-009-0015-8

[20] Nazıroğlu M, Muhamad S, Pecze L. Nanoparticles as potential clinical therapeutic agents in Alzheimer's disease: Focus on selenium nanoparticles. Expert Review of Clinical Pharmacology. 2017;**10**(7):773-782. DOI: 10.1080/17512433.2017.1324781

[21] Nogueira CW, Rocha JBT. Toxicology and pharmacology of selenium: emphasis on synthetic organoselenium compounds. Archives of Toxicology. 2011;**85**(11):1313-1359. DOI: 10.1007/S00204-011-0720-3

[22] Naziroğlu M. TRPM2 cation channels, oxidative stress and neurological diseases: Where are we now? Neurochemical Research. 2011;**36**(3):355-366. DOI: 10.1007/S11064-010-0347-4

[23] Nazıroglu M, Demirdas A. Psychiatric disorders and TRP channels: Focus on psychotropic drugs. Current Neuropharmacology. 2015;**13**(2):248-257. DOI: 10.2174/1570159X13666150304001606

[24] Vural H, Demirin H, Kara Y, Eren I, Delibas N. Alterations of plasma magnesium, copper, zinc, iron and selenium concentrations and some related erythrocyte antioxidant enzyme activities in patients with Alzheimer's disease. Journal of Trace Elements in Medicine and Biology. 2010;**24**(3):169-173. DOI: 10.1016/J.JTEMB.2010.02.002

[25] Rita Cardoso B, Silva Bandeira V, Jacob-Filho W, Franciscato Cozzolino SM. Selenium status in elderly: Relation to cognitive decline. Journal of Trace Elements in Medicine and Biology. 2014;**28**(4):422-426. DOI: 10.1016/J.JTEMB.2014.08.009

[26] Koç ER, İlhan A, Aytürk Z, et al. A comparison of hair and serum trace elements in patients with Alzheimer disease and healthy participants. Turkish Journal of Medical Sciences. 2015;**45**(5):1034-1039. DOI: 10.3906/SAG-1407-67

[27] Balaban H, Nazıroğlu M, Demirci K, Övey İS. The protective role of selenium on scopolamine-induced memory impairment, oxidative stress, and apoptosis in aged rats: The involvement of TRPM2 and TRPV1 channels. Molecular Neurobiology. 2017;**54**(4):2852-2868. DOI: 10.1007/S12035-016-9835-0

[28] Schweizer U, Bräuer AU, Köhrle J, Nitsch R, Savaskan NE. Selenium and brain function: A poorly recognized liaison. Brain Research. Brain Research

Reviews. 2004;**45**(3):164-178. DOI: 10.1016/J.BRAINRESREV.2004.03.004

[29] Fernandes AP, Gandin V. Selenium compounds as therapeutic agents in cancer. Biochimica et Biophysica Acta. 2015;**1850**(8):1642-1660. DOI: 10.1016/J.BBAGEN.2014.10.008

[30] Fan N, Sikand P, Donnelly DF, Ma C, LaMotte RH. Increased Na+ and K+ currents in small mouse dorsal root ganglion neurons after ganglion compression. Journal of Neurophysiology. 2011;**106**(1):211. DOI: 10.1152/JN.00065.2011

[31] Huijun Y, Jiarui L, Tonghan L. Effects of nano red elemental selenium on sodium currents in rat dorsal root ganglion neurons. Annual International Conference of the IEEE Engineering in Medicine and Biology—Proceedings. 2006:896-899. DOI: 10.1109/IEMBS.2006.260758

[32] Amini SM, Mahabadi VP. Selenium nanoparticles role in organ systems functionality and disorder. Nanomedicine Research Journal. 2018;**3**(3):117-124. DOI: 10.22034/NMRJ.2018.03.001

[33] Cong W, Bai R, Li Y, Wang L, Chen C. Biological and medical applications of materials and interfaces selenium nanoparticles as an efficient nanomedicine for the therapy of Huntington's disease selenium nanoparticles as an efficient nanomedicine for the therapy of Huntington's disease. 2019;**11**(38):34725-34735. DOI: 10.1021/acsami.9b12319

[34] Solovyev N, Drobyshev E, Bjørklund G, Dubrovskii Y, Lysiuk R, Rayman MP. Selenium, selenoprotein P, and Alzheimer's disease: Is there a link? Free Radical Biology & Medicine. 2018;**127**:124-133. DOI: 10.1016/J.FREERADBIOMED.2018.02.030

[35] Yuan X, Fu Z, Ji P, et al. Selenium nanoparticles pre-treatment reverse behavioral, oxidative damage, neuronal loss and neurochemical alterations in pentylenetetrazole-induced epileptic seizures in mice. International Journal of Nanomedicine. 2020;**15**:6339. DOI: 10.2147/IJN.S259134

[36] Vicente-Zurdo D, Romero-Sánchez I, Rosales-Conrado N, León-González ME, Madrid Y. Ability of selenium species to inhibit metal-induced Aβ aggregation involved in the development of Alzheimer's disease. Analytical and Bioanalytical Chemistry. 2020;**412**(24):6485-6497. DOI: 10.1007/S00216-020-02644-2

[37] Roman M, Jitaru P, Barbante C. Selenium biochemistry and its role for human health. Metallomics. 2014;**6**(1):25-54. DOI: 10.1039/C3MT00185G

[38] Solovyev N. Selenoprotein P and its potential role in Alzheimer's disease. Hormones (Athens, Greece). 2020;**19**(1):73-79. DOI: 10.1007/S42000-019-00112-W

[39] Ellwanger JH, Franke SIR, Bordin DL, Prá D, Henriques JAP. Biological functions of selenium and its potential influence on Parkinson's disease. Anais da Academia Brasileira de Ciências. 2016;**88**(3):1655-1674. DOI: 10.1590/0001-3765201620150595

[40] Zhang X, Liu RP, Cheng WH, Zhu JH. Prioritized brain selenium retention and selenoprotein expression: Nutritional insights into Parkinson's disease. Mechanisms of Ageing and Development. 2019;**180**:89-96. DOI: 10.1016/J.MAD.2019.04.004

[41] Amani H, Habibey R, Shokri F, et al. Selenium nanoparticles for targeted

stroke therapy through modulation of inflammatory and metabolic signaling. Scientific Reports. 2019;**9**(1):1-15. DOI: 10.1038/s41598-019-42633-9

[42] Khan M, Rutten BPF, Kim MO. MST1 regulates neuronal cell death via JNK/Casp3 signaling pathway in HFD mouse brain and HT22 cells. International Journal of Molecular Sciences. 2019;**20**(10):2504. DOI: 10.3390/IJMS20102504

[43] Nicolas CS, Amici M, Bortolotto ZA, et al. The role of JAK-STAT signaling within the CNS. JAK-STAT. 2013;**2**(1):e22925. DOI: 10.4161/JKST.22925

[44] Gupta J, Fatima MT, Islam Z, Khan RH, Uversky VN, Salahuddin P. Nanoparticle formulations in the diagnosis and therapy of Alzheimer's disease. International Journal of Biological Macromolecules. 2019;**130**:515-526. DOI: 10.1016/J.IJBIOMAC.2019.02.156

[45] Yang L, Wang W, Chen J, Wang N, Zheng G. A comparative study of resveratrol and resveratrol-functional selenium nanoparticles: Inhibiting amyloid β aggregation and reactive oxygen species formation properties. Journal of Biomedical Materials Research. Part A. 2018;**106**(12):3034-3041. DOI: 10.1002/JBM.A.36493

[46] Huo X, Zhang Y, Jin X, Li Y, Zhang L. A novel synthesis of selenium nanoparticles encapsulated PLGA nanospheres with curcumin molecules for the inhibition of amyloid β aggregation in Alzheimer's disease. Journal of Photochemistry and Photobiology. B. 2019;**190**:98-102. DOI: 10.1016/J.JPHOTOBIOL.2018.11.008

[47] Sun D, Zhang W, Yu Q, et al. Chiral penicillamine-modified selenium nanoparticles enantioselectively inhibit metal-induced amyloid β aggregation for treating Alzheimer's disease. Journal of Colloid and Interface Science. 2017;**505**:1001-1010. DOI: 10.1016/J.JCIS.2017.06.083

[48] Yang R, Zheng Y, Wang Q, Zhao L. Curcumin-loaded chitosan–bovine serum albumin nanoparticles potentially enhanced Aβ 42 phagocytosis and modulated macrophage polarization in Alzheimer's disease. Nanoscale Research Letters. 2018;**13**(1):1-9. DOI: 10.1186/S11671-018-2759-Z/FIGURES/6

[49] Yang L, Wang N, Zheng G. Enhanced effect of combining chlorogenic acid on selenium nanoparticles in inhibiting amyloid β aggregation and reactive oxygen species formation in vitro. Nanoscale Research Letters. 2018;**13**(1):265-76. DOI: 10.1186/S11671-018-2720-1

[50] Cong W, Bai R, Li YF, Wang L, Chen C. Selenium nanoparticles as an efficient nanomedicine for the therapy of Huntington's disease. ACS Applied Materials & Interfaces. 2019;**11**(38):34725-34735. DOI: 10.1021/ACSAMI.9B12319

[51] Luo W, Wang Y, Lin F, et al. Selenium-doped carbon quantum dots efficiently ameliorate secondary spinal cord injury via scavenging reactive oxygen species. International Journal of Nanomedicine. 2020;**15**:10113-10125. DOI: 10.2147/IJN.S282985

[52] Chamorro Á, Dirnagl U, Urra X, Planas AM. Neuroprotection in acute stroke: Targeting excitotoxicity, oxidative and nitrosative stress, and inflammation. Lancet Neurology. 2016;**15**(8):869-881. DOI: 10.1016/S1474-4422(16)00114-9

[53] Sekerdag E, Solaroglu I, Gursoy-Ozdemir Y. Cell death mechanisms

in stroke and novel molecular and cellular treatment options. Current Neuropharmacology. 2018;**16**(9): 1396-1415. DOI: 10.2174/1570159X16666180302115544

[54] Turovskaya MV, Gaidin SG, Vedunova MV, Babaev AA, Turovsky EA. BDNF overexpression enhances the preconditioning effect of brief episodes of hypoxia, promoting survival of GABAergic neurons. Neuroscience Bulletin. 2020;**36**(7):733-760. DOI: 10.1007/S12264-020-00480-Z

[55] Gaidin SG, Turovskaya MV, Gavrish MS, et al. The selective BDNF overexpression in neurons protects neuroglial networks against OGD and glutamate-induced excitotoxicity. The International Journal of Neuroscience. 2020;**130**(4):363-383. DOI: 10.1080/00207454.2019.1691205

[56] Turovskaya MV, Zinchenko VP, Babaev AA, Epifanova EA, Tarabykin VS, Turovsky EA. Mutation in the Sip1 transcription factor leads to a disturbance of the preconditioning of AMPA receptors by episodes of hypoxia in neurons of the cerebral cortex due to changes in their activity and subunit composition. The protective effects of interleukin-10. Archives of Biochemistry and Biophysics. 2018;**654**:126-135. DOI: 10.1016/J.ABB.2018.07.019

[57] Ahmed Ragab Abou Zaid O, Mohammed El-sonbaty S, Ezz El-arab Mohammed Barakat W. Ameliorative effect of selenium nanoparticles and ferulic acid on acrylamide-induced neurotoxicity in rats. Annals of Medical and Biomedical Sciences. 2017;**3**(2):35-45. Available from: https://www.researchgate.net/publication/335740590

[58] Turovsky EA, Mal'tseva VN, Sarimov RM, Simakin AV, Gudkov SV, Plotnikov EY. Features of the cytoprotective effect of selenium nanoparticles on primary cortical neurons and astrocytes during oxygen–glucose deprivation and reoxygenation. Scientific Reports. 2022;**12**(1):1-16. DOI: 10.1038/s41598-022-05674-1

[59] Yang J, Huang J, Shen C, et al. Resveratrol treatment in different time-attenuated neuronal apoptosis after oxygen and glucose deprivation/reoxygenation via enhancing the activation of Nrf-2 signaling pathway in vitro. Cell Transplantation. 2018;**27**(12):1789. DOI: 10.1177/0963689718780930

[60] Gao F, Zhao J, Liu P, et al. 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. 2019;**142**:265-276. DOI: 10.1016/j.ijbiomac.2019.09.098

[61] Guo X, Lie Q, Liu Y, Jia Z, Gong Y, Yuan X, et al. Multifunctional selenium quantum dots for the treatment of Alzheimer's disease by reducing Aβ-neurotoxicity and oxidative stress and alleviate neuroinflammation. ACS Applied Materials & Interfaces. 2021;**13**(26):30261-30273

[62] Yang L, Sun J, Xie W, Liu Y, Liu J. Dual-functional selenium nanoparticles bind to and inhibit amyloid β fiber formation in Alzheimer's disease. Journal of Materials Chemistry B. 2017;**5**(30):5954-5967. DOI: 10.1039/C6TB02952C

[63] Gao F, Zhao J, Liu P, et al. 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.

2020;**142**:265-276. DOI: 10.1016/J.IJBIOMAC.2019.09.098

[64] Soleimani Asl S, Amiri I, Samzadeh-kermani A, Abbasalipourkabir R, Gholamigeravand B, Shahidi S. Chitosan-coated Selenium nanoparticles enhance the efficiency of stem cells in the neuroprotection of streptozotocin-induced neurotoxicity in male rats. The International Journal of Biochemistry & Cell Biology. 2021;**141**:106089. DOI: 10.1016/J.BIOCEL.2021.106089

[65] Yue D, Zeng C, Okyere SK, Chen Z, Hu Y. Glycine nano-selenium prevents brain oxidative stress and neurobehavioral abnormalities caused by MPTP in rats. Journal of Trace Elements in Medicine and Biology. 2021;**64**:126680 DOI: 10.1016/J.JTEMB.2020.126680

[66] Salaramoli S, Joshaghani H, Hashemy SI. Selenium effects on oxidative stress-induced calcium signaling pathways in Parkinson's disease. Indian Journal of Clinical Biochemistry. 2022;**37**(3):257-266. DOI: 10.1007/S12291-022-01031-1

[67] Bates GP, Dorsey R, Gusella JF, et al. Huntington disease. Nature Reviews Disease Primers. 2015;**1**(1):1-21. DOI: 10.1038/nrdp.2015.5

[68] Kumar A, Ratan RR. Oxidative stress and Huntington's disease: The good, the bad, and the ugly. Journal of Huntington's Disease. 2016;**5**(3):217-237. DOI: 10.3233/JHD-160205

[69] Al-Chalabi A, Van Den Berg LH, Veldink J. Gene discovery in amyotrophic lateral sclerosis: Implications for clinical management. Nature Reviews. Neurology. 2016;**13**(2):96-104. DOI: 10.1038/nrneurol.2016.182

[70] Paez-Colasante X, Figueroa-Romero C, Rumora AE, et al. Cytoplasmic TDP43 binds microRNAs: New disease targets in amyotrophic lateral sclerosis. Frontiers in Cellular Neuroscience. 2020;**14**:117. DOI: 10.3389/FNCEL.2020.00117/BIBTEX

[71] Deng HX, Hentati A, Tainer JA, et al. Amyotrophic lateral ssclerosis and structural defects in Cu,Zn superoxide dismutase. Science (80-). 1993;**261**(5124):1047-1051. DOI: 10.1126/SCIENCE.8351519

[72] Cunha-Oliveira T, Montezinho L, Mendes C, et al. Oxidative stress in amyotrophic lateral sclerosis: Pathophysiology and opportunities for pharmacological intervention. Oxidative Medicine and Cellular Longevity. 2020;**2020**. DOI: 10.1155/2020/5021694

[73] Amporndanai K, Rogers M, Watanabe S, Yamanaka K, O'Neill PM, Hasnain SS. Novel selenium-based compounds with therapeutic potential for SOD1-linked amyotrophic lateral sclerosis. eBioMedicine. 2020;**59**:102980. DOI: 10.1016/J.EBIOM.2020.102980

[74] Song Z, Liu T, Chen T. Overcoming blood–brain barrier by HER2-targeted nanosystem to suppress glioblastoma cell migration, invasion and tumor growth. Journal of Materials Chemistry B. 2018;**6**(4):568-579. DOI: 10.1039/C7TB02677C

[75] Yin T, Yang L, Liu Y, Zhou X, Sun J, Liu J. Sialic acid (SA)-modified selenium nanoparticles coated with a high blood–brain barrier permeability peptide-B6 peptide for potential use in Alzheimer's disease. Acta Biomaterialia. 2015;**25**:172-183. DOI: 10.1016/J.ACTBIO.2015.06.035

[76] Gholamigeravand B, Shahidi S, Afshar S, et al. Synergistic effects of adipose-derived mesenchymal stem cells and selenium nanoparticles on streptozotocin-induced memory

impairment in the rat. Life Sciences. 2021;**272**:119246. DOI: 10.1016/J.LFS.2021.119246

[77] Pichla M, Bartosz G, Sadowska-Bartosz I. The Antiaggregative and antiamyloidogenic properties of nanoparticles: A promising tool for the treatment and diagnostics of neurodegenerative diseases. Oxidative Medicine and Cellular Longevity. 2020;**2020**. DOI: 10.1155/2020/3534570

[78] Rao S, Lin Y, Lin R, et al. Traditional Chinese medicine active ingredients-based selenium nanoparticles regulate antioxidant selenoproteins for spinal cord injury treatment. Journal of Nanobiotechnology. 2022;**20**(1):1-15. DOI: 10.1186/S12951-022-01490-X

[79] Rao S, Lin Y, Du Y, et al. Designing multifunctionalized selenium nanoparticles to reverse oxidative stress-induced spinal cord injury by attenuating ROS overproduction and mitochondria dysfunction. Journal of Materials Chemistry B. 2019;**7**(16):2648-2656. DOI: 10.1039/C8TB02520G

[80] Khandel P, Yadaw RK, Soni DK, Kanwar L, Shahi SK. Biogenesis of metal nanoparticles and their pharmacological applications: present status and application prospects. Journal of Nanostructure in Chemistry. 2018;**8**(3):217-254. DOI: 10.1007/S40097-018-0267-4

[81] El-Zayat MM, Eraqi MM, Alrefai H, et al. The antimicrobial, antioxidant, and anticancer activity of greenly synthesized selenium and zinc composite nanoparticles using *Ephedra aphylla* extract. Biomolecules. 2021;**11**(3):470. DOI: 10.3390/BIOM11030470

[82] Magaldi S, Mata-Essayag S, Hartung De Capriles C, et al. Well diffusion for antifungal susceptibility testing. International Journal of Infectious Diseases. 2004;**8**(1):39-45. DOI: 10.1016/J.IJID.2003.03.002

[83] Sathiyamoorthy P, Lugasi-Evgi H, Van-Damme P, Abu-Rabia A, Gopas J, Golan-Goldhirsh A. Larvicidal activity in desert plants of the negev and bedouin market plant products. International Journal of Pharmacognosy. 2008;**35**(4):265-273. DOI: 10.1076/PHBI.35.4.265.13314

[84] Al-Hussaini R, Mahasneh AM. Microbial growth and quorum sensing antagonist activities of herbal plants extracts. Molecules. 2009;**14**(9):3425-3435. DOI: 10.3390/MOLECULES14093425

[85] Cuajungco MP, Fagét KY, Huang X, Tanzi RE, Bush AI. Metal chelation as a potential therapy for Alzheimer's disease. Annals of the New York Academy of Sciences. 2000;**920**(1):292-304. DOI: 10.1111/J.1749-6632.2000.TB06938.X

[86] Schomburg L. Dietary selenium and human health. Nutrients. 2016;**9**(1):22. DOI: 10.3390/NU9010022

[87] Zhuang C, Yao D, Li F, Zhang K, Feng Q, Gan Z. Study of micron-thick MgB2 films on niobium substrates. Superconductor Science and Technology. 2007;**20**(3):287. DOI: 10.1088/0953-2048/20/3/030

[88] Kwok JCF, Carulli D, Fawcett JW. In vitro modeling of perineuronal nets: Hyaluronan synthase and link protein are necessary for their formation and integrity. Journal of Neurochemistry. 2010;**114**(5):1447-1459. DOI: 10.1111/J.1471-4159.2010.06878.X

[89] Fedorova TN, Logvinenko AA, Poleshchuk VV, Illarioshkin SN. The

state of systemic oxidative stress during Parkinson's disease. Neurochemical Journal. 2017;**11**(4):340-345. DOI: 10.1134/S1819712417040031

[90] Liu S, Yu W, Lü Y. The causes of new-onset epilepsy and seizures in the elderly. Neuropsychiatric Disease and Treatment. 2016;**12**:1425. DOI: 10.2147/NDT.S107905

[91] Zhu X, Dong J, Han B, et al. Neuronal nitric oxide synthase contributes to PTZ kindling epilepsy-induced hippocampal endoplasmic reticulum stress and oxidative damage. Frontiers in Cellular Neuroscience. 2017;**11**:377. DOI: 10.3389/FNCEL.2017.00377/BIBTEX

[92] Feng L, Wang H, Xue X. Recent progress of nanomedicine in the treatment of central nervous system diseases. Advances in Therapy. 2020;**3**(5):1900159. DOI: 10.1002/ADTP.201900159

[93] Guan B, Yan R, Li R, Zhang X. Selenium as a pleiotropic agent for medical discovery and drug delivery. International Journal of Nanomedicine. 2018;**13**:7473-7490. DOI: 10.2147/IJN.S181343

[94] Sawant VJ, Sawant VJ. Biogenic capped selenium nano rods as naked eye and selective hydrogen peroxide spectrometric sensor. Sensing and Bio-Sensing Research. 2020;**27**(December):100314. DOI: 10.1016/j.sbsr.2019.100314

[95] Nayak V, Singh KR, Singh AK, Singh RP. Potentialities of selenium nanoparticles in biomedical science. New Journal of Chemistry. 2021;**45**(6):2849-2878. DOI: 10.1039/d0nj05884j

[96] Zhang H, Wang T, Qiu W, et al. Monitoring the opening and recovery of the blood-brain barrier with noninvasive molecular imaging by biodegradable ultrasmall Cu2- Se nanoparticles. Nano Letters. 2018;**18**(8):4985-4992. DOI: 10.1021/ACS.NANOLETT.8B01818/SUPPL_FILE/NL8B01818_SI_001.PDF

[97] Cano A, Turowski P, Ettcheto M, et al. Nanomedicine-based technologies and novel biomarkers for the diagnosis and treatment of Alzheimer's disease: From current to future challenges. Journal of Nanobiotechnology. 2021;**19**(1):1-30. DOI: 10.1186/S12951-021-00864-X

[98] Khurana A, Tekula S, Saifi MA, Venkatesh P, Godugu C. Therapeutic applications of selenium nanoparticles. Biomedicine & Pharmacotherapy. 2019;**111**(December):802-812. DOI: 10.1016/j.biopha.2018.12.146

[99] Karthivashan G, Ganesan P, Park SY, Kim JS, Choi DK. Therapeutic strategies and nano-drug delivery applications in management of ageing Alzheimer's disease. Drug Delivery. 2018;**25**(1):307-320. DOI: 10.1080/10717544.2018.1428243

[100] Mukherjee S, Madamsetty VS, Bhattacharya D, Roy Chowdhury S, Paul MK, Mukherjee A. Recent advancements of nanomedicine in neurodegenerative disorders theranostics. Advanced Functional Materials. 2020;**30**(35):2003054. DOI: 10.1002/ADFM.202003054

[101] Yavarpour-Bali H, Pirzadeh M, Ghasemi-Kasman M. Curcumin-loaded nanoparticles: A novel therapeutic strategy in treatment of central nervous system disorders. International Journal of Nanomedicine. 2019;**14**:4449. DOI: 10.2147/IJN.S208332