



Nanozymes for Neurodegenerative Diseases

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Abstract. Neurodegenerative diseases are incurable diseases that get worse as time passes. These diseases are very heterogeneous in nature but have common characteristics like abnormal deposition of protein, glycation, inflammation in particular areas of the brain, and progressive neuronal loss due to oxidative stress. Among these, oxidative stress alone causes a high level of degeneration of neurons. To reduce oxidative stress, natural antioxidants are used but they have some drawbacks like instability, high cost and low reusability. To overcome this, nanozymes are introduced and we have emphasized on major nanozymes whose antioxidant capability has been proven which are gold nanozymes, fullerene, nanoceria, and quantum dots. Gold nanoparticles and their conjugates with other molecules can mimic the enzymatic activity of superoxide dismutase and catalase which decrease the amount of hydrogen peroxide and superoxide radicals in cells. Gold Nanozyme treatment reduces the oxidative stress, nitrite, and sulfhydryl levels in the brain and also rectifies the superoxide dismutase, glutathione, and catalase activity levels. Fullerenols has shown superoxide dismutase activity which was 268 times more effective than mannitol and 37 times more effective than Vitamin E for lipid radicals. Nanoceria has the ability to mimic Superoxide Dismutase as well as catalase activity, can also detoxify peroxynitrite. Quantum dots (QDs) like Graphene Oxide QDs can scavenge the reactive oxygen species and also show indirect activity which alleviates the pathogenesis of the disease. Thus, a nanozyme can be used as an efficient nanomedicine if it is tailored to possess high catalytic activity while eliminating all complications.

Keywords: neurodegenerative diseases · nanozyme · oxidative stress · gold nanoparticles · fullerene · nanoceria · quantum dots

1 Introduction

Neurodegenerative diseases are incurable diseases that get worse as time passes. These diseases cause memory and cognitive impairments and also degrade a person's capability of movement, speech, and breathing [1]. Some of the neurodegenerative diseases include Huntington's disease, Parkinson's disease, Motor neuron diseases, spinocerebellar ataxia (SCA), Alzheimer's disease, Spinal muscular atrophy (SMA), Prion disease, and Amyotrophic lateral sclerosis (ALS). These are very heterogeneous in nature and the underlying cause for a disease is usually unknown, nevertheless, genetic factors are one of the main reasons, for instance, mutations in APP, PSEN1, and PSEN2 genes are

responsible for the occurrence of Alzheimer's disease, mutations in SNCA, PARKIN, LRRK2, DJ-1, PLA2G6, FBXO7, ATP13A2, PINK1 genes leads to Parkinson's disease [2]. Other common reasons include vascular factors like hypertension, diabetes and high blood pressure [3]. At the molecular level as shown in Fig. 1, all neurodegenerative diseases share the common characteristics of abnormal deposition of protein, mitochondrial dysfunction, inflammation in particular areas of the brain, and progressive neuronal loss due to oxidative stress [4, 5]. A person's lifestyle, habits, and diets like heavy sugar diet, smoking, drinking liquor, addiction to psychoactive drugs also lead to neurodegenerative diseases [6, 7].

Our brain consists of many differentiated neurons that occupy different regions and require nearly 20% of the basal metabolic rate to function properly [8]. Every region of the brain has a different capacity to endure oxidative stress also known as Specific neuron vulnerability [9]. The differential capacity to endure oxidative stress plays a key role in causing and amplifying the neurodegenerative disorder. Oxidative Stress is caused by an imbalance generated between the production and detoxification of Reactive Oxygen Species (ROS) like hydrogen peroxide, superoxide radicals, hydroxyl radicals, singlet oxygen. In cells, these ROS are produced by partial reduction of oxygen, and mitochondria are the primary site of ROS production. Growth factor receptor activation can also result in the production of ROS by causing NADPH oxidase to become active, which then oxidises NADPH to produce superoxide. ROS produced by NADPH oxidase play a very crucial role in cell signaling as second messengers, mediating hormonal effects, controlling ion channel function, adipocyte differentiation, reproduction, oxygen sensing, gene expression and cell growth [10]. But, increase in ROS concentrations leads to oxidative modification-induced dysfunctioning of proteins, lipids, and nucleic acids resulting in adverse conditions like ischemia [9] and the onset of other unfavourable conditions in the brain. The brain, which has high oxygen consumption, rich in lipid content, and has high energy demand, is a vulnerable target for oxidative stress [11]. The increased oxidative stress in brain cells can be controlled by natural antioxidant enzymes like superoxide dismutase, catalase, and non-enzymatic compounds like glutathione, vitamin A, B and C, and selenium. However, the amount of ROS generated in a neurodegenerative disorder is too high to be mitigated by the natural antioxidant system of brain cells [12]. Thus, enzyme mimetic nanostructures or nanozymes are being explored as ROS scavengers to be used in therapeutics.

Nanozyme is an important modern tool in discovering solutions to many health problems in diagnostics [13], prognostic [14], and therapeutics [15]. These are the nanomaterials that mimic the enzymatic activity of natural enzymes. Due to their high stability, tunable size, and shape, the broad working range of pH and temperature, low cost, and economic mass production they are preferred over natural enzymes. Most of the nanozymes explored to date mimic the antioxidant property of natural enzymes like superoxide dismutase and catalase. Various nanozymes like Fullerene (& its derivative), nanoceria, gold nanozyme, and quantum dots can be used to alleviate oxidation stress in cells. The antioxidant mimetic activity of nanozymes has been shown to reduce mitochondrial dysfunction [16] and facilitate the clearance of misfolded proteins [17]. Nanozymes not only show ROS scavenging activity but also indirectly restore antioxidant activity [18]. Considering the significance of antioxidant nanozymes, this review

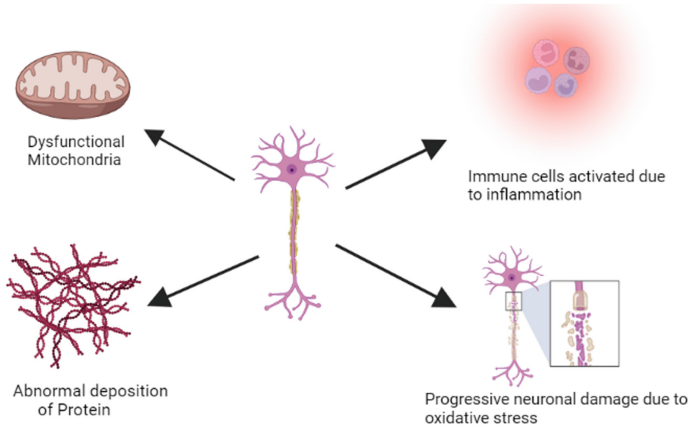


Fig. 1. Common characteristics in neurodegenerative diseases

presents some neurodegenerative diseases where oxidative stress plays a significant role in their occurrence or progression. It further discusses the trends towards exploring nanozymes as a therapeutic alternative to combat the increased oxidative stress for alleviating or reducing the pathogenesis of the disease.

2 Neurodegenerative Diseases

2.1 Alzheimer's Disease

Alzheimer's disease (AD) is most common in elderly people and nearly 5.8 million Americans above the age of 65 are suffering from this disease [19]. It is an irreversible, incurable neurodegenerative disorder that slowly causes loss of memory [20], impeded speech and language [21], mental confusion, and hallucinations [22]. The most accepted hypothesis explains that the pathological aggregation of Amyloid-beta ($A\beta$) protein contributes towards the induction of AD. The $A\beta$ assembles itself into neurotoxic fibrils which get deposited in the hippocampus and other regions of the brain in the form of plaques [23]. In its initial stage, the person only suffers minor memory lapses but as the condition worsens, it slowly impairs cognitive and behavioural abilities such as understanding, attention, language, thinking, and judgement [24]. The $A\beta$ protein mediates its neurodegenerative effects through oxidative stress. Increasing ROS levels causes the oxidation of some enzymes like creatine kinase and glutamine synthetase which are important for neuron and glial functions [25]. This results in enhancement of excitotoxicity and reduction in energy metabolism. As the damage increases, neuronal lesions are formed which further generates superoxide radicals that in turn initiate microglial activation. The slow rate of regeneration of brain and its poor antioxidant status further increases the oxidative stress, thus, aggravating the neurodegeneration process [26]. FDA has approved only four drugs which are galantamine, memantine, donepezil, and rivastigmine for AD's treatment [27]. All these drugs attack the CNS cholinergic pathway or glutamergic pathway providing symptomatic relief only [23, 28]. There are

also drugs like Suvorexant that treats the non-cognitive complications associated with AD like insomnia [29]. Recently, Aducanumab, a monoclonal antibody also approved by FDA can reduce the A β plaques, thus, supposed to reduce the pathogenesis of AD [30].

2.2 Parkinson's Disease

Parkinson's disease (PD) is the second most common disease in elderly people after Alzheimer's disease, with nearly one million Americans suffering from it which is more than the combined strength of people suffering from Lou Gehrig's disease, muscular dystrophy, and multiple sclerosis [31]. Its patients show clinical features like resting tremor, rigidity, postural instability, and bradykinesia. Histological diagnosis is confirmed by the presence of Lewy bodies which contain aggregated α -synuclein [32]. PD's brain unique morphological feature is the disappearance of the darkly stained area in the substantia nigra compacta (SNpc) and locus coeruleus owing to degeneration of noradrenergic neuron in locus coeruleus and dopaminergic neuro-melanin containing neuron in SNpc resulting in decreased levels of dopamine [33]. In more severe cases Lewy bodies can be found in cortex regions like the neocortex, prefrontal cortex, primary motor, and sensory areas which can be clinically observed through features such as dementia and gait problems [34, 35]. Oxidative stress is found to play a crucial role in the progression of degeneration of neurons. A substantial amount of experimental data suggests that dopamine metabolism, high level of iron and calcium in SNpc, low Glutathione level contribute to ROS production which results in dopaminergic neuron loss and further lipid peroxidation and production of other toxic products [36]. Dopamine which is usually released from the dopaminergic neurons is itself very unstable in nature as it can oxidize itself to form free radicals and dopamine quinones. The metabolism of dopamine contributes to enhanced oxidative stress, neural degeneration by aging, and Parkinson's disease. MAO-B and not MAO-A in glial cells become the dominant enzyme to metabolize dopamine and form hydrogen peroxide as a by-product which adds to the oxidative stress. H₂O₂ also reacts with Fe²⁺ of neighbouring dopaminergic neurons to form hydroxyl radical which results in oxidative stress and further neuronal loss [37]. Increasing calcium influx in mitochondria, too, generates ROS as its ATP demands can only be met by more mitochondrial activity, thus more ROS generation [38]. There are no medications that cure this disease but there are some drugs in the market like Levodopa which can alleviate the PD symptoms by converting itself into dopamine after crossing the Blood-Brain Barrier (BBB) thus maintaining the dopamine level, but still, it has some side effects which can be prevented by giving it in combination with L-amino acid decarboxylase inhibitors such as carbidopa and benserazide [39]. Some other medications in use are dopamine agonists like Pramipexole, Ropinirole, Apomorphine, and Rotigotine, MAO-B inhibitors (monoamine oxidase-B inhibitors) like Selegiline, Rasagiline, and Safinamide [40]. But still, all these medications have severe side effects which make them less suitable as a reliable medication. Thus, we need medications that can relieve the symptoms as well as cure the disease.

2.3 Multiple Sclerosis

Multiple sclerosis (MS) is an autoimmune, inflammatory mediated disorder that can be distinguished by the lesions in the central nervous system and show symptoms of physical as well as cognitive disability. Unlike aforementioned neurodegenerative diseases, MS happens usually in the age group of 20–50 and can affect children too [41]. MS is of four types - 1) Relapsing-Remitting MS which is distinguished by the occurrence of acute deterioration in function followed by partial or total recovery [42, 43]. 2) Severely deteriorated patients enter into Second Progressive MS stage which can be distinguished with the features as tiredness, rigidity, weakness, intestinal disorder, urinary disorder and psychological damage [44, 45]. 3) Primary Progressive MS has rapid progression but has fewer lesions with symptoms like Stiffness, weakness, and postural instability [45]. 4) Progressive Relapsing MS is least common and shows symptoms like vision problem, eye pain, intestinal and urinary disorder, sexual dysfunction, dizziness, and also depression [45]. MS works against the CNS myelin antigens, which induce autoreactive T cells, but pathogenesis increases when induction of Th1, Th17 type, and CD8 myelin autoreactive T cells happens [46]. The exact mechanism of MS is still not known but infectious agents, environmental factors, genetic factors, B-cells, microbiome, autoantigens play a role in increasing the autoreactivity which triggers more induction of pathogenic T-cells that attacks the myelin sheath, oligodendrocytes, and neurons [46]. Nevertheless, the role of oxidative stress in disease pathogenesis is certain as most of the inflammatory processes which cause tissue injury are ROS mediated. The formation of lesions which activate microglia and macrophages, also produce a large quantity of ROS such as hydrogen peroxide, superoxide radical, hydroxyl radicals, and nitric oxide [47]. Further, it is known that activated immature myeloid cells also produce ROS and nitric oxide [48]. In autopsy studies also, lesions in the cerebral cortex and white matter, neurodegeneration, and demyelination were found which were linked to the presence of oxidized lipids in the myelin membrane; nuclei of dystrophic glia cells contained oxidized DNA [49]. For the medication, patients with this disease are generally given medicines which suppress their immune system, thus helping in alleviating the symptoms and also slowing the disease progression. But no potent medication is yet available.

3 Nanozymes-Tunable Properties

The physicochemical properties of nanoparticles (NPs) can influence their behaviour (crossing barriers, circulation time, toxicity, etc.) as well as manipulate their catalytic efficiency in *in vivo* systems. A nanozyme can be used as an efficient nanomedicine if it is tailored to possess high catalytic activity while crossing all hurdles. Various properties of nanozymes can affect their interaction and behaviours inside the living system such as their size, concentration, hydrodynamic diameter, zeta potential and conjugation with other particles. Modulation of their physiochemical properties can accelerate their catalytic efficiency at optimum pH and temperature [50, 51]. For example, if we increase the size of nanozyme its catalytic activity would also increase but up to a certain threshold level [52]. Large size NPs possess a low surface to volume ratio thereby reducing the exposed catalytic sites [53] and are more likely to be phagocytosed by macrophages. Morphology of NPs also affects the catalytic activity of nanozyme, as with changed

morphology, a number of facets, and the bond arrangements changes which affect the selectivity of the nanozyme [5]. Nanozyme concentration becomes critical in defining their toxicity and efficacy as very low concentration leads to inefficacy and high concentration leads to toxicity [54]. Circulation time of NPs can be increased in the bloodstream by manipulating zeta potential through a change in pH and electrolyte concentration, which ultimately affects their electrostatic interaction with other proteins and cells [55]. Finally, surface modification of nanoparticles with polymers and biomolecules can influence the permeability, toxicity, biodistribution and activity of nanozymes. For instance, peptide CLPFFD conjugated gold nanoparticles possess the ability to destroy β amyloid but are unable to cross BBB, which can be achieved by conjugation with other peptide sequence THRPPMWSPVWP, as this peptide interacts with the transferin receptor of endothelial cells in BBB and allow the conjugated nanoparticles to cross the BBB [56]. Nanoparticles conjugated with small lectins such as odorranalectin are less immunogenic on intranasal administration [57]. A gold nanoparticle conjugated with ATP (adenosine triphosphate) has comparable activity as natural enzymes and has long-term stability [58]. Thus, Nanozymes can be made versatile with appropriate regulation of their physicochemical properties and can be tuned according to specific need or application.

4 Nanozymes as Therapy for Neurodegenerative Diseases

4.1 Gold Nanozymes

Gold nanoparticle's (AuNPs) ability as nanocarrier has been well studied [59–61]. Their dynamic property of tuning in different sizes and shapes (such as spheres, cubes, rods, cages, stars, polygons, and others), low toxicity, biocompatibility [62] makes them a suitable choice for acting as a nanocarrier across BBB. Gold nanoparticles and their conjugates with other molecules can mimic the enzymatic activity of superoxide dismutase, oxidase, glucose oxidase, peroxidase, and catalase [58, 62]. Gold nanozymes also have a similar mechanism to that of natural enzymes in showing superoxide dismutase activity, which is the elimination of superoxide ions by converting to hydrogen peroxide and oxygen [58]. For catalase mimic activity, first, the Au^{2+} is reduced by the hydrogen peroxide to Au^+ , resulting in proton and oxygen production. Then another hydrogen peroxide combines with oxygen vacancies which oxidize Au^+ to Au^{2+} and give H_2O , completing a clearance cycle of hydrogen peroxide [62]. Generally, in Alzheimer's disease, the deterioration happens in neurons of the hippocampal region, entorhinal cortex, frontal cortex, and amygdala [63]. A group of researchers have shown that Gold Nanozymes can alleviate the oxidative stress and have an anti-inflammatory effect in the cortex and hippocampus region of the brain and also reduce mitochondrial dysfunction which is one of the root causes of neurodegenerative diseases [16]. For the AD model, male Wistar rats were injected with okadaic acids (100 μg) intracerebroventricularly followed by treatment with 20 nm AuNP (dose: 2.5 mg/kg) at every 48 h for 21 days. It was found out that rats treated with only okadaic acid had increased Tau phosphorylation in the hippocampus and the cortex but AuNP treatment maintained the levels at normal. AuNP treatment also reduced the oxidative stress, nitrite, and sulfhydryl levels in the brain which was increased due to okadaic acid, and also rectified the superoxide

dismutase, glutathione, and catalase activity levels [16, 64]. In another study, AuNPs stabilized with glutathione were found to easily cross BBB and inhibit the aggregation of A β 42 fibrils without any toxicity [65]. In Multiple sclerosis (MS), Oligodendrocyte Progenitor Cells (OPCs) are thought to be not able to remyelinate due to cellular stress produced, which also leads to the failure of bioenergetics reactions [66]. But CNM (Clene Nanomedicine) Au-8 which is a multifaceted and highly pure gold nanocrystal can alleviate MS by inducing remyelination as well as OPC differentiation by using a nano catalytic mechanism that involves NAD⁺ and NADH [67, 68]. Thus, gold nanoparticles are very reliable in use and its multipurpose characteristics make them a unique material, whose more applications can be explored in the future.

4.2 Fullerene

Fullerene, a polyhedral carbon cage is arranged in five- and six-membered rings. It has a very impressive cage-like structure with delocalized and pi molecular orbital electrons [69]. It acts as a ROS scavenger by reducing the potential difference between mitochondrial membranes by absorbing excess protons and thereby reduces the superoxide ion production in mitochondria [70]. However, fullerene is water insoluble [71, 72] and need surface functionalization with –COOH (carboxyl) and –OH (hydroxyl) groups or encapsulation in biocompatible liposomes for making it water soluble [73]. These water soluble C60 derivatives have excellent antioxidant properties which are even better than the natural antioxidant enzymes [73]. With the ROS scavenging activity, it can also induce the production of antioxidants in the brain. It has shown its ability in alleviating the pathogenesis of AD, PD, and ALS. In AD, it binds to the core of A β fibrils (LVFF) which is essential for the A β fibril formation and destabilizes the core by preventing fibril formation [74]. As shown in Table 1, C60(OH)₂₄, a fullerene derivative has shown radical scavenging activity which was equivalent to SOD for scavenging superoxide radicals, 268 times more effective than mannitol for scavenging hydroxyl radicals and 37 times more effective than Vitamin E for scavenging lipid radicals respectively [75]. One of the derivative tris malonic acids (C3) can functionally replace the Manganese superoxide dismutase (MnSOD), effectively acting as a SOD mimic [73] and shows inhibiting action on lipid peroxidation [76]. Fullerenols can absorb as well as deactivate the ROS. It also has anti-viral [77], anti-apoptotic [78, 79] activity and helps in enhancement of learning and memory [80]. Fullerene can also penetrate BBB, localize itself into the mitochondrial membrane and accumulate in the lipid bilayer [70, 75]. In PD, Fullerenols contributed to normalization of dopamine synthesis and regulation. It also reduced insoluble alpha-synuclein levels in *Drosophila melanogaster* and showed anti-aggregation characteristics with respect to alpha synuclein proteins [76]. Fullerene derivative C60-OH is very useful in alleviating prion diseases by effectively modulating the microglial activation which happens due to PrP (106–126) and inhibits immoderate production of inflammatory mediators, like TNF- α , IL-1, IL-6, prostaglandin E2, NO, inhibit the expression of COX-2 and inducible NO synthase [81]. It also decreases ROS species and inflammation by increasing the expression of the antioxidant enzymes through Nrf2 expression [81]. So, fullerene shows many effects in many domains and this can be accredited to its cage-like shape, making it a favourable choice for many medical applications.

Table 1. Comparison of the 50% Radical Signal Inhibiting Concentration (IC₅₀) of C₆₀(OH)₂₄ With Specific Free Radical Scavengers [75].

Compound	Superoxide radicals (IC ₅₀ , mM)	Hydroxyl radicals (IC ₅₀ , mM)	Lipid radicals (IC ₅₀ , mM)
C ₆₀ (OH) ₂₄	0.036	0.135	0.495
SOD	0.031	-	-
Mannitol	-	36.3	-
Vit E	-	-	18.4

4.3 Nanoceria

It is a unique earth metal that changes its state between 3+ and 4+ which creates oxygen vacancies causing defects in its crystalline lattice’s surface, which contributes to its much-enhanced antioxidant properties. It has the ability to mimic the catalytic activity of superoxide dismutase, catalase [82, 83] and can detoxify peroxynitrite also [84]. The mechanism of the superoxide dismutase activity of nanoceria is explained in Fig. 2 in which the initial state is ④, where the superoxide ion combines and form ⑤, then an electron transferred from one Ce³⁺ to an oxygen atom to form an electronegative oxygen atom. Subsequently, two electronegative oxygen atoms combine with the two protons to produce hydrogen peroxide and form ⑥. The remaining vacant sites bind with other superoxide ions to form ⑦. Another molecule of hydrogen peroxide is produced when Ce³⁺ changes to Ce⁴⁺ that is ①. Oxygen vacant surface of ① binds to Ce⁴⁺ with hydrogen peroxide to form intermediate ②, which is not stable in nature, and releases two protons changing two Ce⁴⁺ to two Ce³⁺③. Now, ③ is converted to ④ and oxygen is released. This mechanism depicts the significance of Ce³⁺/Ce⁴⁺ ratio for catalytic activity of nanoceria [84].

Some studies also supported the role of different nanoceria formulations in promoting angiogenesis, tissue regeneration, prolonged cell survival, and preventing apoptosis in biological models [85–87]. The underlying reason are the reactions occurring on the surface of nanoceria, which in turn depends on the surface properties like crystal structure, shapes, size, Ce3+/Ce4+ ratio, oxygen vacancies, surface charge, zeta potential, and surface stabilizing agent [88, 89]. For example, citrate stabilized small sized CeNP (5 nm) are deposited more in the liver and spleen as compared to large CeNP particles (55 nm) [90] which are more likely to be phagocytized than smaller ones [91]. Smaller size nanoparticles (3–5 nm) also easily cross the Blood-Brain Barrier as these are detected in the highest level in brain tissue [92]. 3–5 nm size citrate-EDTA stabilized CeNP have been studied in models of neurodegenerative diseases [93–95]. In neurons, they mostly accumulate in the outer membrane of mitochondria and on the inner side of the plasma membrane [96]. Nanoceria was found to be biocompatible when administered in mice with a ROS mediated model of multiple sclerosis [94]. In a yeast model of Parkinson’s disease, with the most effective dose of 50 ng/μL, CeO₂ NP strongly reduced ROS production as well as the formation of cytoplasmic inclusions of alpha synuclein and prevented mitochondrial malfunction [97]. In AD also, CeO₂ NP minimized the

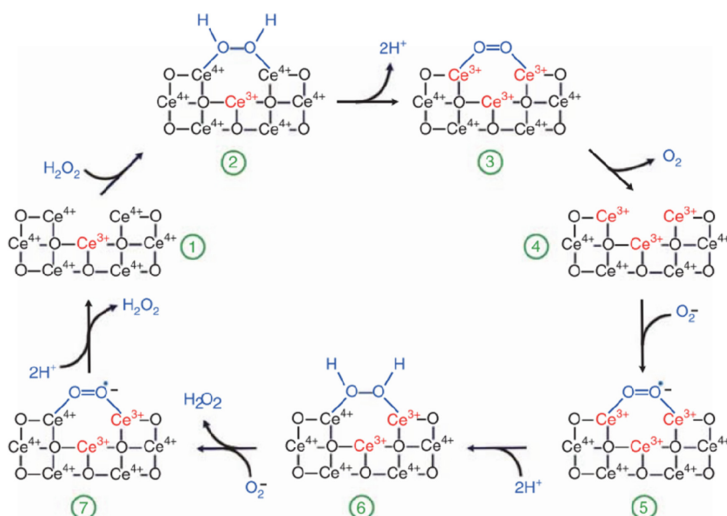


Fig. 2. Proposed mechanism of CeO₂ nanoparticles as superoxide dismutase catalytic ability [84].

fragmentation of mitochondria, peroxynitrate mediated tyrosine nitration and neuronal death caused due to A β [96]. There are several antioxidants like ascorbate, glutathione, α -tocopherol and tetrahydrocurcumin which showed some effect in alleviation of AD models but were proven moderately effective in human trials [98–100]. The possible reason is their poor stability, lack of recycling properties, and translational effectiveness which could possibly be addressed by nanoceria.

4.4 Quantum Dots

Quantum dots (QDs) are very small semiconducting nanoparticles having tunable size with Gaussian emission spectra that would easily be excited by a single wavelength [101]. Surface modification of quantum dots can influence its behaviour heavily [102], thus this property is used to customize QDs according to the needs, like polyethylene glycol-coated QDs [102], folate-conjugated QDs [103], amphiphilic polymer encapsulated QDs [101], Streptivadin coated [104], etc., and also their materials can be of the different type according to the requirement like Cadmium Selenide [105], Graphene oxide [106], Indium Arsenide [107], Lead Sulfide [108], etc. Graphene Oxide QDs with its sp² structure can scavenge the ROS through electron transfer or adduct formation [109]. It also acts by forming iron complexes which inhibit the fenton reaction ($\text{Fe}^{2+} + \text{H}_2\text{O}_2 \rightarrow \text{OH} + \text{OH}^- + \text{Fe}^{3+}$) thus preventing hydroxyl radical formation (Fig. 3). With ROS scavenging activity quantum dots also show indirect activity which alleviates the pathogenesis of the disease. For instance, graphene QDs could prevent α -synucleinopathy in Parkinson's disease as it directly interacted with and caused dis-aggregation of mature fibrils and shortened them from 1 μm to 235 nm [110]. It prevented dissemination of

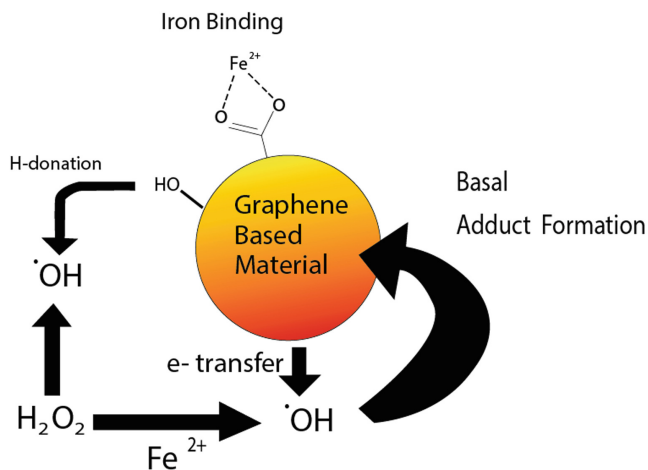


Fig. 3. Antioxidant mechanisms of Graphene based Materials (OH adduct formation on sp^2 -carbon sites, hydrogen donation, iron binding, and electron transfer).

α -synuclein to neighbouring neurons and reduced p- α -synuclein immunoreactivity, pre-formed fibrils (PFF) induced cell toxicity, neuronal death, Lewy Body formation, synaptic loss, mitochondrial dysfunction and can also cross blood-brain barrier [110]. It was found that Graphene QDs showed a reduction of β sheet parts of alpha synuclein in 50 ns of the outer monomer [110]. Graphene oxide QDs also displayed catalase, superoxide dismutase activity as well as regulated apoptosis pathway by MAPK, p53, NOD- like receptor signalling pathway [111]. TPP-MoS₂ (triphenylphosphine-molybdenum disulphide) QD showed that conjugation and functionalization on QDs can enhance its overall ability. For instance, microglia is important against response to the A β fibrils aggregation in AD, and they are of two types: M1 phenotype and M2 phenotype. Former is proinflammatory which is activated by the ROS, inflammatory factors, and A β fibrils and the latter is anti-inflammatory that help in the removal of A β through phagocytosis [112–114]. TPP-MoS₂ QD is designed in such a way that it targeted the microglia's mitochondria and also transformed the M1 phenotypic character into M2 phenotypic character by reducing the expression of CD16/32 and overexpression of CD206 [115]. It showed all the qualities for being an important nanomedicine such as it could escape from lysosomes, prevent mitophagy, mitochondria dysfunction, down regulating inflammatory and apoptotic signalling cytokines, crossing Blood-brain barrier and scavenge ROS [115]. Thus, QDs are novel Nanozymes that can be efficiently used for detection as well as therapeutic purpose.

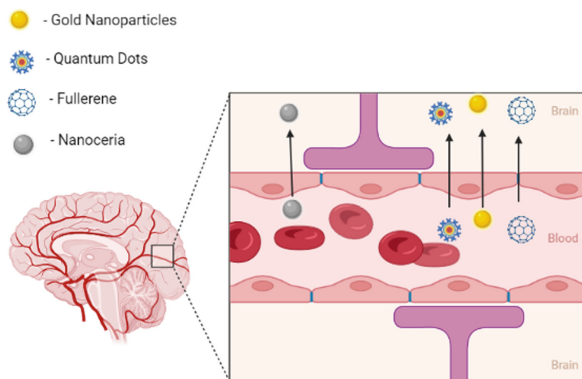


Fig. 4. All the four major nanozymes which are gold nanozymes, fullerene, nanoceria and quantum dots can pass through BBB

5 Conclusion

ROS mediated oxidative stress plays a very significant role in pathogenesis of neurodegenerative diseases directly or indirectly. A rise in their concentrations lead to oxidative modification-induced dysfunctioning of proteins, lipids, and nucleic acids resulting in adverse conditions like ischemia and the onset of other unfavourable conditions in the brain. In this review, we have discussed how oxidative stress accelerates the pathogenesis of neurodegenerative diseases. The role of some nanozymes such as gold nanozymes, fullerene, nanoceria and quantum dots in decreasing the oxidative stress caused by ROS in brain is also discussed. Their ability to mimic superoxide dismutase and catalase has also been elucidated. Any medication that is given to act on brain it has to pass through BBB, and all the four major nanozymes pass through the BBB (Fig. 4). Nanozymes can be a very efficient replacement of natural enzymes. They have shown to have better enzymatic activity than natural enzymes in some instances. Still, natural enzymes have a better specificity than nanozymes and there is also a concern of biosafety of nanozymes. Their toxicity and biodistribution is yet needed to understand carefully, as well as, a need for a deeper understanding of nanozyme's mechanism of how they work. So, in future, if we can regulate the toxicity, biodistribution, concentration and metabolism of nanozymes, they can act as a nanomedicine for the neurodegenerative diseases. A possible future use of nanozymes can also be seen as a supplement because pathogenesis of neurodegenerative diseases starts early but it is diagnosed very late, and oxidative stress not only play a significant role in neurodegenerative diseases but in other diseases also.

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References

1. A.D. Gitler, P. Dhillon, J. Shorter, Neurodegenerative disease: models, mechanisms, and a new hope, *Disease Models & Mechanisms*. 10 (2017), pp. 499–502. DOI: <https://doi.org/10.1242/dmm.030205>.
2. D. Arneson, Y. Zhang, X. Yang, M. Narayanan, Shared mechanisms among neurodegenerative diseases: from genetic factors to gene networks, *Journal of Genetics*. 97 (2018), pp. 795–806. DOI: <https://doi.org/10.1007/s12041-018-0963-3>.
3. P. Hrelia, G. Sita, M. Ziche, E. Ristori, A. Marino, M. Cordaro, R. Molteni, V. Spero, M. Malaguti, F. Morroni, S. Hrelia, Common Protective Strategies in Neurodegenerative Disease: Focusing on Risk Factors to Target the Cellular Redox System, *Oxidative Medicine and Cellular Longevity*. 2020 (2020), pp. 1–18. DOI: <https://doi.org/10.1155/2020/8363245>.
4. S. Majd, J.H. Power, H.J.M. Grantham, Neuronal response in Alzheimer's and Parkinson's disease: the effect of toxic proteins on intracellular pathways, *BMC Neuroscience*. 16 (2015), pp. 69. DOI: <https://doi.org/10.1186/s12868-015-0211-1>.
5. T. Tian, L. Ai, X. Liu, L. Li, J. Li, J. Jiang, Synthesis of Hierarchical FeWO₄ Architectures with {100}-Faceted Nanosheet Assemblies as a Robust Biomimetic Catalyst, *Industrial & Engineering Chemistry Research*. 54 (2015), pp. 1171–1178. DOI: <https://doi.org/10.1021/ie504114v>.
6. C. Ferreira, C. Almeida, S. Tenreiro, A. Quintas, Neuroprotection or Neurotoxicity of Illicit Drugs on Parkinson's Disease, *Life*. 10 (2020), pp. 86. DOI: <https://doi.org/10.3390/life10060086>.
7. A. Popa-Wagner, D. Dumitrascu, B. Capitanescu, E. Petcu, R. Surugiu, W.-H. Fang, D.-A. Dumbrava, Dietary habits, lifestyle factors and neurodegenerative diseases, *Neural Regeneration Research*. 15 (2020), pp. 394. DOI: <https://doi.org/10.4103/1673-5374.266045>.
8. G. Cenini, A. Lloret, R. Cascella, Oxidative Stress and Mitochondrial Damage in Neurodegenerative Diseases: From Molecular Mechanisms to Targeted Therapies, *Oxidative Medicine and Cellular Longevity*. 2020 (2020), pp. 1–2. DOI: <https://doi.org/10.1155/2020/1270256>.
9. Wang, Selective neuronal vulnerability to oxidative stress in the brain, *Frontiers in Aging Neuroscience*. (2010). DOI: <https://doi.org/10.3389/fnagi.2010.00012>.
10. M. Sedeek, R. Nasrallah, R.M. Touyz, R.L. Hébert, NADPH Oxidases, Reactive Oxygen Species, and the Kidney: Friend and Foe, *Journal of the American Society of Nephrology*. 24 (2013), pp. 1512–1518. DOI: <https://doi.org/10.1681/ASN.2012111112>.
11. A.J. Hulbert, R. Pamplona, R. Buffenstein, W.A. Buttemer, Life and Death: Metabolic Rate, Membrane Composition, and Life Span of Animals, *Physiological Reviews*. 87 (2007), pp. 1175–1213. DOI: <https://doi.org/10.1152/physrev.00047.2006>.
12. B. Uttara, A. Singh, P. Zamboni, R. Mahajan, Oxidative Stress and Neurodegenerative Diseases: A Review of Upstream and Downstream Antioxidant Therapeutic Options, *Current Neuropharmacology*. 7 (2009), pp. 65–74. DOI: <https://doi.org/10.2174/1570159090787602823>.
13. P. Wang, T. Wang, J. Hong, X. Yan, M. Liang, Nanozymes: A New Disease Imaging Strategy, *Frontiers in Bioengineering and Biotechnology*. 8 (2020). DOI: <https://doi.org/10.3389/fbioe.2020.00015>.
14. B. Jiang, L. Yan, J. Zhang, M. Zhou, G. Shi, X. Tian, K. Fan, C. Hao, X. Yan, Biomimetic Nanosynthesis of the Cobalt Nanozyme in SP94-Ferritin Nanocages for Prognostic Diagnosis of Hepatocellular Carcinoma, *ACS Applied Materials & Interfaces*. 11 (2019), pp. 9747–9755. DOI: <https://doi.org/10.1021/acsami.8b20942>.

15. D.P. Cormode, L. Gao, H. Koo, Emerging Biomedical Applications of Enzyme-Like Catalytic Nanomaterials, *Trends in Biotechnology*. 36 (2018), pp. 15–29. DOI: <https://doi.org/10.1016/j.tibtech.2017.09.006>.
16. N. dos Santos Tramontin, S. da Silva, R. Arruda, K.S. Ugioni, P.B. Canteiro, G. de Bem Silveira, C. Mendes, P.C.L. Silveira, A.P. Muller, Gold Nanoparticles Treatment Reverses Brain Damage in Alzheimer's Disease Model, *Molecular Neurobiology*. 57 (2020), pp. 926–936. DOI: <https://doi.org/10.1007/s12035-019-01780-w>.
17. Y. Zhao, J. Cai, Z. Liu, Y. Li, C. Zheng, Y. Zheng, Q. Chen, H. Chen, F. Ma, Y. An, L. Xiao, C. Jiang, L. Shi, C. Kang, Y. Liu, Nanocomposites Inhibit the Formation, Mitigate the Neurotoxicity, and Facilitate the Removal of β -Amyloid Aggregates in Alzheimer's Disease Mice, *Nano Letters*. 19 (2019), pp. 674–683. DOI: <https://doi.org/10.1021/acs.nanolett.8b03644>.
18. H. Wu, H. Liao, F. Li, J. Lee, P. Hu, W. Shao, X. Li, D. Ling, Bioactive ROS-scavenging nanozymes for regenerative medicine: Reestablishing the antioxidant firewall, *Nano Select*. 1 (2020), pp. 285–297. DOI: <https://doi.org/10.1002/nano.202000021>.
19. 2020 Alzheimer's disease facts and figures, *Alzheimer's & Dementia*. 16 (2020), pp. 391–460. DOI: <https://doi.org/10.1002/alz.12068>.
20. H. Jahn, Memory loss in Alzheimer's disease, *Dialogues in Clinical Neuroscience*. 15 (2013), pp. 445–454. DOI: <https://doi.org/10.31887/DCNS.2013.15.4/hjahn>.
21. S. Ferris, M. Farlow, Language impairment in Alzheimer disease and benefits of acetylcholinesterase inhibitors, *Clinical Interventions in Aging*. (2013), p. 1007. DOI: <https://doi.org/10.2147/CIA.S39959>.
22. P.-Y. Chiu, M.-H. Hsu, C.-W. Wang, C.-T. Tsai, M.-C. Pai, Visual hallucinations in Alzheimer's disease is significantly associated with clinical diagnostic features of dementia with Lewy bodies, *PLOS ONE*. 12 (2017), DOI: <https://doi.org/10.1371/journal.pone.0186886>.
23. T.-Q. Li, L.-W. Huang, X. Xue, Introduction: Nanomedicine in the Brain, in: *Nanomedicine in Brain Diseases*, Springer Singapore, (2019), pp. 1–28. DOI: https://doi.org/10.1007/978-981-13-8731-9_1.
24. Anil Kumar, Jaskirat Sidhu, Amandeep Goyal, Jack W. Tsao, *Alzheimer Disease*, StatPearls Publishing, 2022.
25. W.J. Huang, X. Zhang, W.W. Chen, Role of oxidative stress in Alzheimer's disease, *Biomedical Reports*. 4 (2016), pp. 519–522. DOI: <https://doi.org/10.3892/br.2016.630>.
26. S. Manoharan, G.J. Guillemín, R.S. Abiramasundari, M.M. Essa, M. Akbar, M.D. Akbar, The Role of Reactive Oxygen Species in the Pathogenesis of Alzheimer's Disease, Parkinson's Disease, and Huntington's Disease: A Mini Review, *Oxidative Medicine and Cellular Longevity*. 2016 (2016), pp. 1–15. DOI: <https://doi.org/10.1155/2016/8590578>.
27. Alzheimer's Disease Treatment: Medications, Therapies, and Care, (n.d.). DOI: <https://www.webmd.com/alzheimers/guide/alzheimers-disease-treatment-overview> (accessed July 28, 2022).
28. W.V. Graham, A. Bonito-Oliva, T.P. Sakmar, Update on Alzheimer's Disease Therapy and Prevention Strategies, *Annual Review of Medicine*. 68 (2017), pp. 413–430. DOI: <https://doi.org/10.1146/annurev-med-042915-103753>.
29. W.J. Herring, P. Ceesay, E. Snyder, D. Bliwise, K. Budd, J. Hutzelmann, J. Stevens, C. Lines, D. Michelson, Polysomnographic assessment of suvorexant in patients with probable Alzheimer's disease dementia and insomnia: a randomized trial, *Alzheimer's & Dementia*. 16 (2020), pp. 541–551. DOI: <https://doi.org/10.1002/alz.12035>.
30. J. Cummings, S. Salloway, Aducanumab: Appropriate use recommendations, *Alzheimer's & Dementia*. 18 (2022), pp. 531–533. DOI: <https://doi.org/10.1002/alz.12444>.
31. Statistics | Parkinson's Foundation, (n.d.). DOI: <https://www.parkinson.org/Understanding-Parkinsons/Statistics> (accessed July 28, 2022).

32. A.H. Schapira, P. Jenner, Etiology and pathogenesis of Parkinson's disease, *Movement Disorders*. 26 (2011), pp. 1049–1055. DOI: <https://doi.org/10.1002/mds.23732>.
33. D.W. Dickson, *Parkinson's Disease and Parkinsonism: Neuropathology*, Cold Spring Harbor Perspectives in Medicine. 2 (2012) a009258–a009258. DOI: <https://doi.org/10.1101/cshperspect.a009258>.
34. H. Braak, K. del Tredici, U. Rüb, R.A.I. de Vos, E.N.H. Jansen Steur, E. Braak, staging of brain pathology related to sporadic Parkinson's disease, *Neurobiology of Aging*. 24 (2003), pp. 197–211. DOI: [https://doi.org/10.1016/S0197-4580\(02\)00065-9](https://doi.org/10.1016/S0197-4580(02)00065-9).
35. N. Pavese, M. Rivero-Bosch, S.J. Lewis, D.J. Brooks, P3.024 Progression of monoaminergic dysfunction in Parkinson's disease: a longitudinal 18F-Dopa PET study, *Parkinsonism & Related Disorders*. 15 (2009), pp. S154. DOI: [https://doi.org/10.1016/S1353-8020\(09\)70588-7](https://doi.org/10.1016/S1353-8020(09)70588-7).
36. P. Jenner, C.W. Olanow, The pathogenesis of cell death in Parkinson's disease, *Neurology*. 66 (2006), pp. S24–S36. DOI: https://doi.org/10.1212/WNL.66.10_suppl_4.S24.
37. M.J. Kumar, J.K. Andersen, Perspectives on MAO-B in Aging and Neurological Disease: Where Do We Go From Here? *Molecular Neurobiology*. 30 (2004), pp. 077–090. DOI: <https://doi.org/10.1385/MN:30:1:077>.
38. D.J. Surmeier, J.N. Guzman, J. Sanchez-Padilla, P.T. Schumacker, The role of calcium and mitochondrial oxidant stress in the loss of substantia nigra pars compacta dopaminergic neurons in Parkinson's disease, *Neuroscience*. 198 (2011), pp. 221–231. DOI: <https://doi.org/10.1016/j.neuroscience.2011.08.045>.
39. Levodopa (L-Dopa) - StatPearls - NCBI Bookshelf, (n.d.). DOI: <https://www.ncbi.nlm.nih.gov/books/NBK482140/> (accessed July 28, 2022).
40. Approved Medications | American Parkinson Disease Assoc., (n.d.). DOI: <https://www.apdaparkinson.org/what-is-parkinsons/treatment-medication/medication/> (accessed July 28, 2022).
41. Multiple Sclerosis: Facts, Statistics, and You, (n.d.). DOI: <https://www.healthline.com/health/multiple-sclerosis/facts-statistics-infographic> (accessed July 28, 2022).
42. M. Kheradmand, M. Afshari, M.M. Nasehi, I. Aghaei, M. Shabani, F. Farshidi, M. Moosazadeh, Prevalence of subtypes of multiple sclerosis and the most common clinical symptoms in Iranian patients: A meta-analysis, *Clinical and Experimental Neuroimmunology*. 10 (2019), pp. 33–40. DOI: <https://doi.org/10.1111/cen3.12489>.
43. K.A. McKay, V. Kwan, T. Duggan, H. Tremlett, Risk Factors Associated with the Onset of Relapsing-Remitting and Primary Progressive Multiple Sclerosis: A Systematic Review, *BioMed Research International*. 2015 (2015), pp. 1–11. DOI: <https://doi.org/10.1155/2015/817238>.
44. M. Koch, E. Kingwell, P. Rieckmann, H. Tremlett, The natural history of secondary progressive multiple sclerosis, *Journal of Neurology, Neurosurgery & Psychiatry*. 81 (2010), pp. 1039–1043. DOI: <https://doi.org/10.1136/jnnp.2010.208173>.
45. N. Ghasemi, S. Razavi, E. Nikzad, Multiple Sclerosis: Pathogenesis, Symptoms, Diagnoses and Cell-Based Therapy, *Cell Journal (Yakhteh)*. 19 (2017), p. 1. DOI: <https://doi.org/10.22074/CELLJ.2016.4867>.
46. D. Miljković, I. Spasojević, Multiple Sclerosis: Molecular Mechanisms and Therapeutic Opportunities, *Antioxidants & Redox Signaling*. 19 (2013), pp. 2286–2334. DOI: <https://doi.org/10.1089/ars.2012.5068>.
47. K. Ohl, K. Tenbrock, M. Kipp, Oxidative stress in multiple sclerosis: Central and peripheral mode of action, *Exp Neurol*. 277 (2016), pp. 58–67. DOI: <https://doi.org/10.1016/J.EXPNEUROL.2015.11.010>.
48. Q. Zhang, M. Fujino, J. Xu, X.K. Li, The Role and Potential Therapeutic Application of Myeloid-Derived Suppressor Cells in allo-and autoimmunity, *Mediators of Inflammation*. 2015 (2015). DOI: <https://doi.org/10.1155/2015/421927>.

49. L. Haider, M.T. Fischer, J.M. Frischer, J. Bauer, R. Höftberger, G. Botond, H. Esterbauer, C.J. Binder, J.L. Witztum, H. Lassmann, Oxidative damage in multiple sclerosis lesions, *Brain*. 134 (2011), pp. 1914–1924. DOI: <https://doi.org/10.1093/BRAIN/AWR128>.
50. J. Wu, X. Wang, Q. Wang, Z. Lou, S. Li, Y. Zhu, L. Qin, H. Wei, Nanomaterials with enzyme-like characteristics (nanozymes): next-generation artificial enzymes (II), *Chemical Society Reviews*. 48 (2019), pp. 1004–1076. DOI: <https://doi.org/10.1039/C8CS00457A>.
51. Z. Zhang, Y. Li, X. Zhang, J. Liu, Molecularly imprinted nanozymes with faster catalytic activity and better specificity, *Nanoscale*. 11 (2019), pp. 4854–4863. DOI: <https://doi.org/10.1039/C8NR09816F>.
52. Z. Xi, W. Gao, X. Xia, Size Effect in Pd–Ir Core-Shell Nanoparticles as Nanozymes, *ChemBioChem*. 21 (2020), pp. 2440–2444. DOI: <https://doi.org/10.1002/cbic.202000147>.
53. Z. Wang, R. Zhang, X. Yan, K. Fan, Structure and activity of nanozymes: Inspirations for de novo design of nanozymes, *Materials Today*. 41 (2020), pp. 81–119. DOI: <https://doi.org/10.1016/j.mattod.2020.08.020>.
54. C. Cavaliere, L. Tramontano, D. Fiorenza, V. Alfano, M. Aiello, M. Salvatore, Gliosis and Neurodegenerative Diseases: The Role of PET and MR Imaging, *Frontiers in Cellular Neuroscience*. 14 (2020). DOI: <https://doi.org/10.3389/fncel.2020.00075>.
55. B. Sarmiento, D. Mazzaglia, M.C. Bonferoni, A.P. Neto, M. do Céu Monteiro, V. Seabra, Effect of chitosan coating in overcoming the phagocytosis of insulin loaded solid lipid nanoparticles by mononuclear phagocyte system, *Carbohydrate Polymers*. 84 (2011), pp. 919–925. DOI: <https://doi.org/10.1016/j.carbpol.2010.12.042>.
56. R. Prades, S. Guerrero, E. Araya, C. Molina, E. Salas, E. Zurita, J. Selva, G. Egea, C. López-Iglesias, M. Teixidó, M.J. Kogan, E. Giralt, Delivery of gold nanoparticles to the brain by conjugation with a peptide that recognizes the transferrin receptor, *Biomaterials*. 33 (2012), pp. 7194–7205. DOI: <https://doi.org/10.1016/j.biomaterials.2012.06.063>.
57. Z. Wen, Z. Yan, R. He, Z. Pang, L. Guo, Y. Qian, X. Jiang, L. Fang, Brain targeting and toxicity study of odorranalectin-conjugated nanoparticles following intranasal administration, *Drug Delivery*. 18 (2011), pp. 555–561. DOI: <https://doi.org/10.3109/10717544.2011.596583>.
58. M. Sharifi, K. Faryabi, A.J. Talaei, M.S. Shekha, M. Ale-Ebrahim, A. Salihi, N.M.Q. Nanakali, F.M. Aziz, B. Rasti, A. Hasan, M. Falahati, Antioxidant properties of gold nanozyme: A review, *Journal of Molecular Liquids*. 297 (2020), pp. 112004. DOI: <https://doi.org/10.1016/j.molliq.2019.112004>.
59. G. Han, P. Ghosh, V.M. Rotello, Functionalized gold nanoparticles for drug delivery, *Nanomedicine*. 2 (2007), pp. 113–123. DOI: <https://doi.org/10.2217/17435889.2.1.113>.
60. M. Khongkow, T. Yata, S. Boonrungsiman, U.R. Ruktanonchai, D. Graham, K. Namdee, Surface modification of gold nanoparticles with neuron-targeted exosome for enhanced blood–brain barrier penetration, *Scientific Reports*. 9 (2019), pp. 8278. DOI: <https://doi.org/10.1038/s41598-019-44569-6>.
61. D. Teleanu, C. Chircov, A. Grumezescu, A. Volceanov, R. Teleanu, Blood-Brain Delivery Methods Using Nanotechnology, *Pharmaceutics*. 10 (2018), pp. 269. DOI: <https://doi.org/10.3390/pharmaceutics10040269>.
62. J. Lou-Franco, B. Das, C. Elliott, C. Cao, Gold Nanozymes: From Concept to Biomedical Applications, *Nano-Micro Letters*. 13 (2021), pp. 10. DOI: <https://doi.org/10.1007/s40820-020-00532-z>.
63. X. Chen, C. Guo, J. Kong, Oxidative stress in neurodegenerative diseases, *Neural Regen Res*. 7 (2012), pp. 376–385. DOI: <https://doi.org/10.3969/J.ISSN.1673-5374.2012.05.009>.
64. T.H. Lai, C.H. Chung, B.H. Chen, C.F. Hung, B.S. Inbaraj, M.C. Ma, H.M. Chen, C.J. Tsou, P.H. Wu, W. bin Wu, Gold Nanoparticles Compromise TNF- α -Induced Endothelial Cell Adhesion Molecule Expression Through NF- κ B and Protein Degradation Pathways and Reduce Neointima Formation in A Rat Carotid Balloon Injury Model, *J Biomed Nanotechnology*. 12 (2016), pp. 2185–2201. DOI: <https://doi.org/10.1166/JBN.2016.2315>.

65. K. Hou, J. Zhao, H. Wang, B. Li, K. Li, X. Shi, K. Wan, J. Ai, J. Lv, D. Wang, Q. Huang, H. Wang, Q. Cao, S. Liu, Z. Tang, Chiral gold nanoparticles enantioselectively rescue memory deficits in a mouse model of Alzheimer's disease, *Nature Communications*. 11 (2020), pp. 4790. DOI: <https://doi.org/10.1038/s41467-020-18525-2>.
66. V.K.C. Nimmagadda, T.K. Makar, K. Chandrasekaran, A.R. Sagi, J. Ray, J.W. Russell, C.T. Bever, SIRT1 and NAD⁺ precursors: Therapeutic targets in multiple sclerosis a review, *Journal of Neuroimmunology*. 304 (2017), pp. 29–34. DOI: <https://doi.org/10.1016/j.jneuroim.2016.07.007>.
67. W. Penberthy, I. Tsunoda, The Importance of NAD in Multiple Sclerosis, *Current Pharmaceutical Design*. 15 (2009), pp. 64–99. DOI: <https://doi.org/10.2174/138161209787185751>.
68. A.P. Robinson, J.Z. Zhang, H.E. Titus, M. Karl, M. Merzliakov, A.R. Dorfman, S. Karlik, M.G. Stewart, R.K. Watt, B.D. Facer, J.D. Facer, N.D. Christian, K.S. Ho, M.T. Hotchkiss, M.G. Mortenson, R.H. Miller, S.D. Miller, Nanocatalytic activity of clean-surfaced, faceted nanocrystalline gold enhances remyelination in animal models of multiple sclerosis, *Scientific Reports*. 10 (2020), pp. 1936. DOI: <https://doi.org/10.1038/s41598-020-58709-w>.
69. A. Dellinger, Z. Zhou, J. Connor, A. Madhankumar, S. Pamujula, C.M. Sayes, C.L. Kepley, Application of fullerenes in nanomedicine: an update, *Nanomedicine*. 8 (2013), pp. 1191–1208. DOI: <https://doi.org/10.2217/nnm.13.99>.
70. V.A. Chistyakov, Yu.O. Smirnova, E. v. Prazdnova, A. v. Soldatov, Possible Mechanisms of Fullerene C₆₀ Antioxidant Action, *BioMed Research International*. 2013 (2013), pp. 1–4. DOI: <https://doi.org/10.1155/2013/821498>.
71. R. Injac, M. Prijatelj, B. Strukelj, Fullerenol nanoparticles: toxicity and antioxidant activity, *Methods Mol Biol*. 1028 (2013), pp. 75–100. DOI: https://doi.org/10.1007/978-1-62703-475-3_5.
72. A. Mateo-Alonso, D. Bonifazi, M. Prato, Functionalization and applications of [60] fullerene, in: *Carbon Nanotechnology*, Elsevier, 2006: pp. 155–189. DOI: <https://doi.org/10.1016/B978-044451855-2/50010-3>.
73. M. Lens, L. Medenica, U. Citeresi, Antioxidative capacity of C60 (buckminsterfullerene) and newly synthesized fulleropyrrolidine derivatives encapsulated in liposomes, *Biotechnology and Applied Biochemistry*. 51 (2008), pp. 135. DOI: <https://doi.org/10.1042/BA20080007>.
74. L. Xie, Y. Luo, D. Lin, W. Xi, X. Yang, G. Wei, The molecular mechanism of fullerene-inhibited aggregation of Alzheimer's β -amyloid peptide fragment, *Nanoscale*. 6 (2014), pp. 9752–9762. DOI: <https://doi.org/10.1039/C4NR01005A>.
75. X. Cai, H. Jia, Z. Liu, B. Hou, C. Luo, Z. Feng, W. Li, J. Liu, Polyhydroxylated fullerene derivative C₆₀(OH)₂₄ prevents mitochondrial dysfunction and oxidative damage in an MPP⁺-induced cellular model of Parkinson's disease, *Journal of Neuroscience Research*. 86 (2008), pp. 3622–3634. DOI: <https://doi.org/10.1002/jnr.21805>.
76. L.L. Dugan, E.G. Lovett, K.L. Quick, J. Lotharius, T.T. Lin, K.L. O'Malley, Fullerene-based antioxidants and neurodegenerative disorders, *Parkinsonism & Related Disorders*. 7 (2001), pp. 243–246. DOI: [https://doi.org/10.1016/S1353-8020\(00\)00064-X](https://doi.org/10.1016/S1353-8020(00)00064-X).
77. M. Shoji, E. Takahashi, D. Hatakeyama, Y. Iwai, Y. Morita, R. Shirayama, N. Echigo, H. Kido, S. Nakamura, T. Mashino, T. Okutani, T. Kuzuhara, Anti-Influenza Activity of C60 Fullerene Derivatives, *PLoS ONE*. 8 (2013), pp. e66337. DOI: <https://doi.org/10.1371/journal.pone.0066337>.
78. S. Ye, M. Chen, Y. Jiang, M. Chen, Y. Wang, Z. Hou, L. Ren, T. Zhou, Polyhydroxylated fullerene attenuates oxidative stress-induced apoptosis via a fortifying Nrf2-regulated cellular antioxidant defence system, *International Journal of Nanomedicine*. (2014), p. 2073. DOI: <https://doi.org/10.2147/IJN.S56973>.

79. M.S. Misirkic, B.M. Todorovic-Markovic, L.M. Vucicevic, K.D. Janjetovic, V.R. Jokanovic, M.D. Dramicanin, Z.M. Markovic, V.S. Trajkovic, The protection of cells from nitric oxide-mediated apoptotic death by mechanochemically synthesized fullerene (C60) nanoparticles, *Biomaterials*. 30 (2009), pp. 2319–2328. DOI: <https://doi.org/10.1016/j.biomaterials.2009.01.023>.
80. L. Chen, Y. Miao, L. Chen, J. Xu, X. Wang, H. Zhao, Y. Shen, Y. Hu, Y. Bian, Y. Shen, J. Chen, Y. Zha, L.-P. Wen, M. Wang, The role of low levels of fullerene C60 nanocrystals on enhanced learning and memory of rats through persistent CaMKII activation, *Biomaterials*. 35 (2014), pp. 9269–9279. DOI: <https://doi.org/10.1016/j.biomaterials.2014.07.030>.
81. S. Ye, T. Zhou, D. Pan, Y. Lai, P. Yang, M. Chen, Y. Wang, Z. Hou, L. Ren, Y. Jiang, Fullerene C₆₀ Derivatives Attenuated Microglia-Mediated Prion Peptide Neurotoxicity, *Journal of Biomedical Nanotechnology*. 12 (2016), pp. 1820–1833. DOI: <https://doi.org/10.1166/jbn.2016.2281>.
82. C. Korsvik, S. Patil, S. Seal, W.T. Self, Superoxide dismutase mimetic properties exhibited by vacancy engineered ceria nanoparticles, *Chemical Communications*. (2007), p. 1056. DOI: <https://doi.org/10.1039/b615134e>.
83. T. Pirmohamed, J.M. Dowding, S. Singh, B. Wasserman, E. Heckert, A.S. Karakoti, J.E.S. King, S. Seal, W.T. Self, Nanoceria exhibit redox state-dependent catalase mimetic activity, *Chemical Communications*. 46 (2010), pp. 2736. DOI: <https://doi.org/10.1039/b922024k>.
84. Y. Huang, J. Ren, X. Qu, Nanozymes: Classification, Catalytic Mechanisms, Activity Regulation, and Applications, *Chem Rev*. 119 (2019), pp. 4357–4412. DOI: <https://doi.org/10.1021/ACS.CHEMREV.8B00672>.
85. S. Chigurupati, M.R. Mughal, E. Okun, S. Das, A. Kumar, M. McCaffery, S. Seal, M.P. Mattson, Effects of cerium oxide nanoparticles on the growth of keratinocytes, fibroblasts and vascular endothelial cells in cutaneous wound healing, *Biomaterials*. 34 (2013), pp. 2194–2201. DOI: <https://doi.org/10.1016/j.biomaterials.2012.11.061>.
86. S. Das, S. Chigurupati, J. Dowding, P. Munusamy, D.R. Baer, J.F. McGinnis, M.P. Mattson, W. Self, S. Seal, Therapeutic potential of nanoceria in regenerative medicine, *MRS Bulletin*. 39 (2014), pp. 976–983. DOI: <https://doi.org/10.1557/mrs.2014.221>.
87. S. Das, S. Singh, J.M. Dowding, S. Oommen, A. Kumar, T.X.T. Sayle, S. Saraf, C.R. Patra, N.E. Vlahakis, D.C. Sayle, W.T. Self, S. Seal, The induction of angiogenesis by cerium oxide nanoparticles through the modulation of oxygen in intracellular environments, *Biomaterials*. 33 (2012), pp. 7746–7755. DOI: <https://doi.org/10.1016/j.biomaterials.2012.07.019>.
88. A. Estevez, M. Ganesana, J. Trentini, J. Olson, G. Li, Y. Boateng, J. Lipps, S. Yablonski, W. Donnelly, J. Leiter, J. Erlichman, Antioxidant Enzyme-Mimetic Activity and Neuroprotective Effects of Cerium Oxide Nanoparticles Stabilized with Various Ratios of Citric Acid and EDTA, *Biomolecules*. 9 (2019), pp. 562. DOI: <https://doi.org/10.3390/biom9100562>.
89. E. Grulke, K. Reed, M. Beck, X. Huang, A. Cormack, S. Seal, Nanoceria: factors affecting its pro- and anti-oxidant properties, *Environ. Sci.: Nano*. 1 (2014), pp. 429–444. DOI: <https://doi.org/10.1039/C4EN00105B>.
90. R.A. Yokel, M.T. Tseng, M. Dan, J.M. Unrine, U.M. Graham, P. Wu, E.A. Grulke, Biodistribution and biopersistence of ceria engineered nanomaterials: size dependence, *Nanomedicine: Nanotechnology, Biology and Medicine*. 9 (2013), pp. 398–407. DOI: <https://doi.org/10.1016/j.nano.2012.08.002>.
91. C. He, Y. Hu, L. Yin, C. Tang, C. Yin, Effects of particle size and surface charge on cellular uptake and biodistribution of polymeric nanoparticles, *Biomaterials*. 31 (2010), pp. 3657–3666. DOI: <https://doi.org/10.1016/j.biomaterials.2010.01.065>.
92. Y.A. Komarova, K. Kruse, D. Mehta, A.B. Malik, Protein Interactions at Endothelial Junctions and Signaling Mechanisms Regulating Endothelial Permeability, *Circulation Research*. 120 (2017), pp. 179–206. DOI: <https://doi.org/10.1161/CIRCRESAHA.116.306534>.

93. W. DeCoteau, K.L. Heckman, A.Y. Estevez, K.J. Reed, W. Costanzo, D. Sandford, P. Studlack, J. Clauss, E. Nichols, J. Lipps, M. Parker, B. Hays-Erlichman, J.C. Leiter, J.S. Erlichman, Cerium oxide nanoparticles with antioxidant properties ameliorate strength and prolong life in mouse model of amyotrophic lateral sclerosis, *Nanomedicine: Nanotechnology, Biology and Medicine*. 12 (2016), pp. 2311–2320. DOI: <https://doi.org/10.1016/j.nano.2016.06.009>.
94. K.L. Heckman, A.Y. Estevez, W. DeCoteau, S. Vangellow, S. Ribeiro, J. Chiarenzelli, B. Hays-Erlichman, J.S. Erlichman, Variable in Vivo and in Vitro Biological Effects of Cerium Oxide Nanoparticle Formulations, *Frontiers in Pharmacology*. 10 (2020). DOI: <https://doi.org/10.3389/fphar.2019.01599>.
95. F.M. Ribeiro, M.M. de Oliveira, S. Singh, T.S. Sakthivel, C.J. Neal, S. Seal, T. Ueda-Nakamura, S. de O.S. Lautenschlager, C.V. Nakamura, Ceria Nanoparticles Decrease UVA-Induced Fibroblast Death Through Cell Redox Regulation Leading to Cell Survival, Migration and Proliferation, *Frontiers in Bioengineering and Biotechnology*. 8 (2020). DOI: <https://doi.org/10.3389/fbioe.2020.577557>.
96. J.M. Dowding, W. Song, K. Bossy, A. Karakoti, A. Kumar, A. Kim, B. Bossy, S. Seal, M.H. Ellisman, G. Perkins, W.T. Self, E. Bossy-Wetzel, Cerium oxide nanoparticles protect against A β -induced mitochondrial fragmentation and neuronal cell death, *Cell Death & Differentiation*. 21 (2014), pp. 1622–1632. DOI: <https://doi.org/10.1038/cdd.2014.72>.
97. R. Ruotolo, G. de Giorgio, I. Minato, M. Bianchi, O. Bussolati, N. Marmiroli, Cerium Oxide Nanoparticles Rescue α -Synuclein-Induced Toxicity in a Yeast Model of Parkinson's Disease, *Nanomaterials*. 10 (2020), pp. 235. DOI: <https://doi.org/10.3390/nano10020235>.
98. R.K. Chaturvedi, M.F. Beal, Mitochondrial Approaches for Neuroprotection, *Ann N Y Acad Sci*. 1147 (2008), pp. 395–412. DOI: <https://doi.org/10.1196/annals.1427.027>.
99. Y. Gilgun-Sherki, E. Melamed, D. Offen, Oxidative stress induced-neurodegenerative diseases: the need for antioxidants that penetrate the blood brain barrier, *Neuropharmacology*. 40 (2001), pp. 959–975. DOI: [https://doi.org/10.1016/S0028-3908\(01\)00019-3](https://doi.org/10.1016/S0028-3908(01)00019-3).
100. B. Frei, Efficacy of Dietary Antioxidants to Prevent Oxidative Damage and Inhibit Chronic Disease, *The Journal of Nutrition*. 134 (2004), pp. 3196S–3198S. DOI: <https://doi.org/10.1093/jn/134.11.3196S>.
101. S.J. Rosenthal, J.C. Chang, O. Kovtun, J.R. McBride, I.D. Tomlinson, Biocompatible Quantum Dots for Biological Applications, *Chemistry & Biology*. 18 (2011), pp. 10–24. DOI: <https://doi.org/10.1016/J.CHEMBIOL.2010.11.013>.
102. M. Zhang, B.P. Bishop, N.L. Thompson, K. Hildahl, B. Dang, O. Mironchuk, N. Chen, R. Aoki, V.C. Holmberg, E. Nance, Quantum dot cellular uptake and toxicity in the developing brain: implications for use as imaging probes, *Nanoscale Advances*. 1 (2019), pp. 3424–3442. DOI: <https://doi.org/10.1039/C9NA00334G>.
103. D.J. Bharali, D.W. Lucey, H. Jayakumar, H.E. Pudavar, P.N. Prasad, Folate-Receptor-Mediated Delivery of InP Quantum Dots for Bioimaging Using Confocal and Two-Photon Microscopy, *J Am Chem Soc*. 127 (2005), pp. 11364–11371. DOI: <https://doi.org/10.1021/ja051455x>.
104. J. Wang, W.H. Yong, Y. Sun, P.T. Vernier, H.P. Koeffler, M.A. Gundersen, L. Marcu, Receptor-targeted quantum dots: fluorescent probes for brain tumor diagnosis, *Journal of Biomedical Optics*. 12 (2007), pp. 044021. DOI: <https://doi.org/10.1117/1.2764463>.
105. A.C. Carter, S.A. Majetich, Surface Effects on the Properties of Cadmium Selenide Quantum Dots, *MRS Proceedings*. 286 (1992), pp. 81. DOI: <https://doi.org/10.1557/PROC-286-81>.
106. L. Li, Graphene Oxide: Graphene Quantum Dot Nanocomposite for Better Memristic Switching Behaviors, *Nanomaterials*. 10 (2020), pp. 1448. DOI: <https://doi.org/10.3390/nano10081448>.

107. S. Li, K. Koike, Ground state splitting of vertically stacked indium arsenide self-assembled quantum dots, *Applied Physics Letters*. 81 (2002), pp. 3594–3596. DOI: <https://doi.org/10.1063/1.1515365>.
108. J. Peterson, T. Krauss, Fluorescence from Individual Lead Sulfide Quantum Dots, *ECS Meeting Abstracts*. MA2005-01 (2006), p. 970. DOI: <https://doi.org/10.1149/MA2005-01/28/970>.
109. Y. Qiu, Z. Wang, A.C.E. Owens, I. Kulaots, Y. Chen, A.B. Kane, R.H. Hurt, Antioxidant chemistry of graphene-based materials and its role in oxidation protection technology, *Nanoscale*. 6 (2014), pp. 11744–11755. DOI: <https://doi.org/10.1039/C4NR03275F>.
110. D. Kim, J.M. Yoo, H. Hwang, J. Lee, S.H. Lee, S.P. Yun, M.J. Park, M. Lee, S. Choi, S.H. Kwon, S. Lee, S.-H. Kwon, S. Kim, Y.J. Park, M. Kinoshita, Y.-H. Lee, S. Shin, S.R. Paik, S.J. Lee, S. Lee, B.H. Hong, H.S. Ko, Graphene quantum dots prevent α -synucleinopathy in Parkinson's disease, *Nature Nanotechnology*. 13 (2018), pp. 812–818. DOI: <https://doi.org/10.1038/s41565-018-0179-y>.
111. A. Sun, L. Mu, X. Hu, Graphene Oxide Quantum Dots as Novel Nanozymes for Alcohol Intoxication, *ACS Applied Materials & Interfaces*. 9 (2017), pp. 12241–12252. DOI: <https://doi.org/10.1021/acsami.7b00306>.
112. X. Lan, X. Han, Q. Li, Q.-W. Yang, J. Wang, Modulators of microglial activation and polarization after intracerebral hemorrhage, *Nature Reviews Neurology*. 13 (2017), pp. 420–433. DOI: <https://doi.org/10.1038/nrneurol.2017.69>.
113. N.K. Bennett, R. Chmielowski, D.S. Abdelhamid, J.J. Faig, N. Francis, J. Baum, Z.P. Pang, K.E. Uhrich, P. v. Moghe, Polymer brain-nanotherapeutics for multipronged inhibition of microglial α -synuclein aggregation, activation, and neurotoxicity, *Biomaterials*. 111 (2016), pp. 179–189. DOI: <https://doi.org/10.1016/j.biomaterials.2016.10.001>.
114. Y. Lu, Z. Guo, Y. Zhang, C. Li, Y. Zhang, Q. Guo, Q. Chen, X. Chen, X. He, L. Liu, C. Ruan, T. Sun, B. Ji, W. Lu, C. Jiang, Microenvironment Remodeling Micelles for Alzheimer's Disease Therapy by Early Modulation of Activated Microglia, *Advanced Science*. 6 (2019), pp. 1801586. DOI: <https://doi.org/10.1002/advs.201801586>.
115. C. Ren, D. Li, Q. Zhou, X. Hu, Mitochondria-targeted TPP-MoS₂ with dual enzyme activity provides efficient neuroprotection through M1/M2 microglial polarization in an Alzheimer's disease model, *Biomaterials*. 232 (2020), pp. 119752. DOI: <https://doi.org/10.1016/j.biomaterials.2019.119752>.

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