Oxidative Stress in Alzheimer’s Disease: Targeting with Nanotechnology

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Abstract — Oxidative stress has been strongly implicated in the pathogenesis of Alzheimer’s disease (AD), a major neurodegenerative disease prevalent among the aging population. The consequences of AD include but not limited to progressive dementia, cognitive impairment, and development of neuropsychiatric symptoms. There is no cure for AD despite of the psychological, social, and economical impacts of the disease on the individual and the society. The current lines of palliative treatment are also unsatisfactory. Several antioxidants based clinical trials have been performed recently in attempts to develop novel therapies. These endeavors, however, failed to produce any clinically successful outcome which could be attributed to the poor solubility, inefficacious delivery, and poor bioavialability of antioxidants. Nanotechnology holds the promise of unleashing the optimum potentials of antioxidant therapy for NDDs by overcoming the above limitations. In this mini-review, we summerize the (i) biology of oxidative stress, (ii) oxidative stress in AD, and (iii) antioxidant therapies. Finally, we highlights the prospects of nanotechnology for modulating oxidative stress in Alzheimer’s disease.

Keywords — Alzheimer’s disease (AD), antioxidant, neuro-degenerative disease (NDD), nanotechnology, nanoparticle (NP), oxidative stress, reactive oxygen species (ROS).

1. BIOLOGY OF OXIDATIVE STRESS

The biochemical steady state of the cell is characteristically maintained by the reduction-oxidation (redox) reactions associated with the gain (reduction) or loss (oxidation) of electron(s) [Figure-1]. The biomolecules, depending on their roles in the redox processes, are classified either as a reducing agent (electron donor) or as an oxidizing agent (electron acceptor) [1]. Although it appears as a simpler chemical phenomenon, the redox mechanism in the nature is not always complete. Incomplete reduction leads to the generation of two very unstable and reactive chemical species, such as (i) radical species/ free radicals (FR) and (ii) nonradical species/ reactive metabolites (RM) [2]. The FR and RM have significant biological roles in a myriad of signaling pathways, and therefore the cellular levels of these entities should be tightly regulated. Failure of this regulation in the cell induces a biochemical/physiological state described as oxidative stress [3, 4].

![Redox reaction](image)

Fig. 1. Redox (reduction-oxidation) reaction.

By definition, oxidative stress refers to the state of imbalance between production of free radicals and reactive metabolites (oxidants) and their elimination by protective mechanisms (antioxidants) [5]. The internal cellular microenvironment (cellular metabolism, peroxisomes, and enzymes etc.) as well as the external macro-environment (UV radiation, heat shock, chemicals, and exercise etc.) are sources of oxidative stress mediated by reactive oxygen species (ROS) as shown in Figure 2 [3, 6].

1.1 Reactive Oxygen Species

Reactive oxygen species (ROS) are one of the several reactive chemical species that include reactive nitrogen species (RNS), reactive sulfur species (RSS), and reactive chlorine species...
Most ROS and RNS are produced during intracellular metabolism involving the mitochondrial respiratory chain [7]. The defective autophagy of mitochondria is also a major source of ROS [8]. The synthesis of ATP in the mitochondria requires multistep oxidative phosphorylation along the electron transport chain. During this metabolic process oxygen molecule is reduced to water by accepting four electrons [9]. Although aerobic respiration is very efficient, 1-5% of oxygen consumed forms the superoxide anion (\(\cdot O_2^-\)), which is converted into hydrogen peroxide and water by an antioxidant enzyme superoxide dismutase (Figure 3) [10]. The excessive superoxide anions (\(\cdot O_2^-\)) subsequently form hydrogen peroxide (\(H_2O_2\)), hydroxyl radical (\(\cdot OH\)) and other organic peroxides, which are members of the ROS [11]. Molecules such as \(\cdot O_2^-\) and \(\cdot OH\) are the free radicals with an unpaired electron in their outer orbits whereas \(H_2O_2\) is a reactive metabolite. ROS are highly unstable chemical species capable of interacting with other radicals or molecules. Nitric oxide (NO) is an example of the RNS produced by the mitochondrial respiratory chain. The ROS and RNS have both beneficial and harmful effects depending on their natures and cellular concentrations.

1.2 Biological Effects of ROS

ROS play vital roles in stimulation of the signal transduction pathways in response to environmental conditions by interacting with organic molecules. They participate in cellular events such as cell cycle regulation [12], enzyme activation [13, 14], protein modification etc. [15]. Nitrous oxide is an important signaling molecule that regulates relaxation and proliferation of vascular smooth muscle cells, leukocytes adhesion, platelets aggregation, angiogenesis, etc. [16]. Also, bacteria or virus infected cells are destroyed by phagocytosis with an oxidative burst of ROS [17].

Although ROS have important cellular functions at low concentrations, they can have many harmful effects at higher concentrations. ROS produced over a long time, under stress, can damage the cell structures, impair functions, induce diseases and enhance aging. The extent of damage depends on the intracellular concentration of ROS, and the equilibrium between ROS and antioxidants. When balance is lost, oxidative stress is generated leading to damage of many intracellular molecules (Figure 4). ROS specifically damage DNA/RNA, lipids, and proteins. In DNA, ROS can cause nicks and malfunctions in DNA repair mechanisms. These include DNA strand breaks, point mutations, aberrant DNA cross-linking, and mutations in proto-oncogenes and tumor suppressing genes [18]. DNA oxidation by ROS, specifically the hydroxyl radical, also generates a substance, 8-hydroxy-2-deoxyguanosine (8-OHdG), which induces further mutations in DNA enhancing both aging and carcinogenesis [19]. The cell membrane is a phospholipid bilayer composed of polyunsaturated lipids susceptible to peroxidation by ROS. This leads to increased permeability of the cell membrane resulting in cellular damages and cell apoptosis [20]. Proteins are most affected by high levels of ROS. They suffer from the accumulation of carbonyl and thiol groups, which can be converted to sulfur radicals by ROS. This oxidative stress induced modifications lead to alteration in the protein structures, and hence loss of vital functions [21, 22].

1.3 Antioxidant

Oxygen is important for cells, but it is dangerous when present in excess; so it is kept under check by a complex system that monitors and regulates the uptake of oxygen. Antioxidants are the cell defense mechanisms that scavenge reactive species like ROS. Antioxidants co-evolved along with aerobic metabolism to counteract oxidative damage. They possess anti-inflammatory, anti-atherosclerotic, anti-mutagenic, anti-carcinogenic, anti-bacterial, anti-viral capabilities. There are two groups of antioxidants: endogenous antioxidants and exogenous antioxidants [23, 24]. Endogenous antioxidants include glutathione, alpha-lipoic acid, coenzyme Q etc. Glutathione is the main endogenous antioxidant produced by the cells and it helps to protect the cell from ROS like free radicals and peroxides. Exogenous antioxidants include natural antioxidants and synthetic antioxidants. Natural antioxidants

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**Fig. 2.** Balance of oxidative stress and antioxidant defense mechanism.

**Fig. 3.** ROS formation and their elimination by endogenous mechanisms.
can be either enzymatic or non-enzymatic (Figure 2). Superoxide dismutase (SOD), Catalase and Glutathione Peroxidase (GSHPxs) are three important antioxidant enzymes (Figure 3) [25]. Three types of SODs exist in human cells: copper-zinc SOD (Cu-Zn SOD, SOD1), manganese SOD (Mn-SOD, SOD2), and extracellular SOD (EC-SOD, SOD3); all three types can dismutate 2 superoxide anions into hydrogen peroxide and oxygen [26]. Catalase can then break down H$_2$O$_2$ into water.

![Oxidative Homeostasis Diagram](image)

**Fig. 4.** Fates of cellular ROS and biological effects.

2. OXIDATIVE STRESS AND ALZHEIMER’S DISEASE

ROS are linked to a variety of diseases such as cancers, diabetes, cardiovascular diseases, chronic obstructive pulmonary disease (COPD), asthma, allergies and inflammatory diseases, immune-mediated diseases, NDDs and aging. Neuropathological diseases comprise a condition characterized by the loss of neuronal integrity at structural level and clinically manifested by impairment of the motor (ataxia) and sensory (dementia) activities at functional level. A positive correlation has been established between the incidences of NDDs and aging [27]. Alzheimer’s disease (AD), Parkinson’s disease (PD), Huntington’s disease, multiple sclerosis (MS) and amyotrophic lateral sclerosis (ALS) are few most common NDDs. AD is the most prevalent among the NDDs. Epidemiological studies indicate that AD affects as many as 5.2 million people of all ages in the US, and nearly 5 million of them are 65 years of age or older. It is anticipated that the number of people with AD will rise to 16 million by 2050 [28]. Currently there is no cure for treatment of AD. Only five drugs (donepezil, galantamine, memantine, rivastigmine, and tacrine) have been approved for symptomatic management of the disease. Most of these drugs are positive neurotransmission modulators (acetylcholine esterase inhibitors) and have toxic side effects. Considering the pivotal role of oxidative stress in neurodegenerative pathogenesis of AD, attempts have been made to understand the underlying mechanism and subsequent development of suitable antioxidant therapy.

2.1 Oxidative Damages

The pathological basis of AD and neuronal oxidative stress can be explained in terms of mitochondrial dysfunction and apoptosis. Both ROS and RNS equally contribute for the oxidative stress mediated neural degeneration and involve superoxide anion, hydrogen peroxide, hydroxyl radical, and nitric oxide (NO). The reaction between nitric oxide with the superoxide anion produces peroxynitrite that decomposes to form the highly reactive hydroxyl radical. The reactive species predispose the neurons to a hypersensitive environment and induce neurotoxicity [29, 30]. The excitatory amino acids, neurotransmitters, and unsaturated fatty acids in the brain are susceptible to the oxidative attacks resulting in the production of many toxic metabolites that damage the neuronal structures. The low level of antioxidant activity in the brain aggravate the oxidative damage process. The glial cells and neurons are very sensitive to oxidative stress because of their higher metabolic needs and post-mitotic nature. The antioxidant threshold and regeneration ability of the brain cells further decline with age and the oxidative damage becomes phenomenal [31].

2.2 Factors of Oxidative Stress

The defective metabolism of redox metals, genetic abnormalities and dietary factors are considered the contributing factors for NDDs related to oxidative stress [32]. Several metalloenzymes associated with different catalytic pathways are responsible for generation of ROS from the interaction of redox metals (e.g. iron, copper and zinc) and oxygen via the Fenton reaction (Figure-3) [33]. The concentration of redox metal in the brain increases with age which in turn exposes the aging brain to oxidative stress and neurodegeneration [34]. Defective iron metabolism has been established in all forms of NDDs listed above. Also the signature proteins in NDDs such as β amyloid (AD), α-synuclein (PD), Cu-Zn superoxide dismutase (ALS) present redox metal for improper interaction with oxygen facilitating ROS formation [35-37]. The genetic mutation disease that requires regular supplementation of iron as in case of hemochromatosis has been proposed as a risk factor for development of neuropathology from iron related oxidative stress [38]. Mutations of the genetic element such as vitagenes have been proposed to be associated with neurodegeneration [39]. These genes encode heat-shock proteins, thioredoxin and the sirtuin protein systems and assist in preserving cellular homeostasis during stressful conditions. Environmental factors and diets containing low level of antioxidants and higher amount of saturated fats, alcohol etc. increases the chances of oxidative damage and development of AD [40].

2.3 Oxidative Stress and Neuropathogenesis
AD is the most common NDD prevalent among the elderly population and clinically manifested by progressive dementia and cognitive impairment. Gross and histopathology reveals two distinct but functionally related patterns in the Alzheimer’s disease brain; (i) a significant loss of nerve cells and synapse in different parts of the brain and (ii) extracellular accumulation of Aβ-amyloid (senile plaques) and intracellular formation of neurofibrillary tangles [41]. The role of oxidative stress in the pathogenesis of AD is strongly established [42]. The deleterious effects of oxidative attack in AD are associated with lipid peroxidation, protein oxidation, advanced glycation, DNA damage, aberrant metal oxidation, misfolded protein accumulation, and inflammatory damage etc. Consequently the concentrations of several byproducts of oxidative damages are increased in the brain, cerebrospinal fluid, and other tissue fluids. The markers of lipid peroxidation such as 4-hydroxyhexenal, F2-isoprostane, F4-neuroprostane are increased in the brain [43, 44]. Peroxidation of lipids can also liberate reactive electrophiles (e.g. acrolein) that affect mitochondrial respiration [45]. Protein derivatives from oxidation (protein carbonyls), nitrilation (3- nitrotyrosine) and glycation are elevated in the CSF [46]. Similarly, the nucleic acid oxidation product 8-hydroxyguanine (8-OHG) is increased in the CSF [47].

The positive correlation between Aβ and oxidative stress is clearly established [48]. Oxidative stress induces increased Aβ accumulation which damages the mitochondrial integrity and promotes increased ROS formation and apoptosis (Figure-5). All these events stimulate Aβ production and a positive auto feedback loop is set up. Neuronal cell apoptosis in AD has been closely linked to oxidative stress supported by the findings that many antiapoptotic proteins (HSP 60, Vimentin, TRX-1 and GRX-1) are oxidized upon treatment with Aβ peptide, and the level of glutathione (GSH) is also lowered [49]. Aβ being a metalloprotein binds with transition metals to promote H2O2 synthesis which mediates toxic hydroxyl radical formation and perturbs calcium homeostasis. The calcium dysregulation event leads to further ROS formation and ultimately favoring a neuronal excitotoxicity response. Increased metal concentration and oxidative stress affect Aβ deposition and formation of toxic oligomers [50]. The association of genetic risk factor ApoE4 has been confirmed in the development of AD [51]. Advanced glycation products present in Aβ and neurofibrillary tangles induce release of many neuroinflammatory products and affects AD pathogenesis [52].

2.4 Antioxidants in the Brain

Oxidative stress is a natural phenomenon in aging and other age-related neurodegenerative changes. Although there are many antioxidants present in the brain tissues and fluids, they are present in a significantly lower level. Some of the antioxidants in the brain include glutathione (GSH), vitamins E and C, and selenium (Figure-2). GSH is the most important antioxidant in the brain as well as other tissues. Glutathione Peroxidase catalyzes the binding of GSH with oxidized molecules and form glutathione disulphide (GSSH) which is reduced back to GSH by glutathione reductase (GR). The ratio of GSH/GSSH is lowered in AD which predisposes the brain to oxidative damage [53]. Vitamin E (α-tocopherol) and vitamin C (ascorbic acid) are well known for their antioxidant properties. Vitamin E is fat-soluble and therefore believed to prevent lipid peroxidation and associated oxidative damage [54]. Similar results have also been found for vitamin C [55]. Therefore, both of these vitamins have been highly recommended for AD. Selenium (Se), an essential micronutrient, is a cofactor for antioxidant enzymes like glutathione peroxidase and thioredoxin reductase. However, the role of selenium in relation to AD remains inconclusive [56].

3. ANTIOXIDANT THERAPIES FOR ALZHEIMER’S DISEASE

The drug discovery for NDDs like AD has been very challenging for many reasons. The disease is very complex with multifactorial etiological basis and has a prolonged course of development. There is significant idiosyncratic variation in the onset, nature, and pathogenesis of the disease. The involvement of different signaling pathways and factors make the identification of a druggable target very difficult. Also, no suitable animal model of AD is available. Based on the understanding of the disease, the ideal treatment for AD and any other NDD should be able to mitigate the clinical symptoms as well as offer neuroprotection. Oxidative stress in AD is associated with neuronal dysfunction, apoptosis, and pathophysioLOGIC mechanisms. Therefore, antioxidants can be employed as therapeutic agents for symptomatic management and cure of AD. Antioxidants can be employed at two levels, (i) upstream therapy (e.g. vitamin E, vitamin C, β carotene etc.) for preventive measure [57] and (ii) downstream therapy (e.g. EGb761, CPI-1189, 17-estradiol etc.) for post-oxidative events [58, 59].
3.1 Current Progress

Significant efforts have been made towards the development of novel antioxidant therapies for Alzheimer’s disease. However, a satisfactory antioxidant therapy for AD is yet to be found because of inconsistent results [49]. We highlight the major findings of these studies in this section to draw relevance to our discussion. Supplementation of vitamins (vitamin E and/or vitamin C) in AD patients did neither improve the cognitive skills nor reduce the level of Aβ42 or phosphorylated-tau despite reduction of the level of lipid peroxidation in the CSF [60]. In some studies the patients even demonstrated adverse effect of administration of antioxidant vitamins compared to the control group [61]. Selenium at high dose has been shown to improve several cognitive parameters when given with vitamin E [62]. The antioxidant properties of ‘curcumin’ from Curcuma Long Lin inhibit Aβ aggregation in vitro and in animal models but failed to reproduce similar effects in clinical trials [63]. This could be due to poor absorption of curcumin from gastrointestinal tract and subsequent passage through blood brain barrier. Trail with lapidated curcumin improved overall uptake and significantly decreased the plasma level of Aβ40. Studies with EGB761, extracted from Ginkgo biloba leaves, did not improve cognitive ability in AD patients [64]. Effects of Coenzyme Q-10 (CoQ10) and its analogue MitoQ are tested which targets the mitochondrial oxidative stress but the results are not encouraging [65]. Treatment of women having AD with estrogen therapy did not improve the clinical conditions in any way [66]. Proline-rich polypeptides from colostrum (Colostrinin) demonstrated improved cognitive behavior during early stage of the disease; colostrinin has been proposed to increase activity of GPx and GR in vitro without affecting the lipid peroxidation [67].

3.2 Challenges

The efficacy of antioxidant therapies to counteract oxidative stress in neurodegenerative diseases is well known. But, most of the antioxidants fail to produce desire effect because of (i) poor aqueous solubility, (ii) insufficient bioavailability, (iii) short half-life and (iv) non-optimal concentration at the site of action [68]. These limitations point towards an inefficient antioxidant delivery system for the brain. Brain, unlike other organs, is separated from the peripheral circulation by the blood-brain barrier (BBB) system [69]. BBB serves as a selective filter and regulates the passage of specific molecule in and out of the brain. In order to overcome these hurdles, nanotechnology can be employed to develop an efficient antioxidant delivery system for the brain.

4. Nanotechnology for Oxidative Stress

The advent of nanotechnology has significantly impacted the modern biomedical research for development of imaging and diagnostic tools as well as novel therapeutics for clinical applications. AD is a multifactorial disease with critical roles of ROS for pathogenesis. The use of nanotechnology to deal with oxidative stress is relevant. However, the full scope of nanomedicine as oxidative stress modulator is not yet realized to derive optimum therapeutic benefits against disease like AD. Several nano-formulations have been successfully developed for brain tumor. Nanoparticles (NPs) are key players of the nanotechnology approach. There are two fundamental ways how the NPs elicit the desired antioxidant effects. First, the NPs may act as a carrier molecule (nanocarrier) to transport natural antioxidants such as vitamin E, β-carotene, and curcumin etc. to the desired sites [70]. Second, specific NPs (e.g. silver nanoparticles, cerium oxide, titanium dioxide etc.) have intrinsic antioxidant properties to counteract the cellular oxidative stress environment [71, 72]. These synthetic antioxidants can scavenge both ROS and RNS to minimize the extent of cellular oxidative damage. The antioxidant are dissolved, entrapped, encapsulated or attached to the nanoparticle matrix for delivery [73]. Several nanotechnology based formulation have been used for diagnosis, imaging and targeting of NDDs [74, 75].

4.1 Characteristics of NPs

NPs are defined as particulate dispersions or solid particles with size range of 10-1000 nm. The benefits of using NPs are many folds, such as target specificity, greater safety and biocompatibility, minimal toxicity, and increased potency etc. [76]. The three important characteristics of NPs that influence drug delivery are particle size, surface properties, and loading capacity [73]. The smaller size nanoparticle are preferred over larger ones for drug delivery into brain as they can easily pass through the BBB [76]. The smaller NPs also have larger surface area and the drug molecules are present closer to the surface which facilitates faster release. Larger NPs entrap the drug within the core resulting in slower release [73]. The surface property of NPs such as hydrophobicity determines their clearance from the circulation by opsonin-mediated phagocytosis. A more hydrophilic coating of the NPs prevent phagocytosis and increase concentration in the circulation [77]. The drug loading capacity of the NPs should be high to reduce carrier overload. Along with this the carrier molecules should be nontoxic, non-immunogenic, biocompatible, and biodegradable (Figure 6). Biodegradability and solubility of the nanoparticle matrix is important for drug release. Albumin based nanoparticle fulfills many of these criteria for drug delivery and perfectly suited for therapeutic release of antioxidants in diseases like AD [78].

4.2 Brain-Targeted Delivery with NPs

Enhanced delivery of the drugs, antioxidants, or imaging agents to the brain with nanocarriers can be achieved by targeting any...
of the four endogenous mechanisms, such as (i) carrier-mediated transporter proteins, (ii) transcellular lipophilic pathway, (iii) receptor-mediated transcytosis, and (iv) adsorptive transcytosis (Figure 7). The appropriate modification of NP surface (coating or conjugation) is critical in this regard. Several structurally modified nanoparticles have been developed, and an up-to-date review of the NP-based delivery system targeting the brain is available [79]. A few examples of surface coated NP for this purpose include PEG-coated NPs, thiamine-coated NPs, transferrin coated NPs etc. NPs can also be polymer (albumin, chitosan, heparin etc.) conjugated or could be a fullerenol-cytotoxic conjugate. Other methods include liposomal technology, angiopipep (nineteen amino acids containing peptide vector) system or LipoBridge technology (facilitates temporary opening of the tight junctions of the BBB) [79].

4.3 Oxidative Stress Modulating Nanotherapeutics in AD

The primary objectives of nanotechnology and the conventional approaches are similar (promote neuroprotection and enhance neuroregeneration) when it comes to the use of antioxidant for AD. However, nanotechnology outcompetes the other by the promises of targeted drug delivery and improved bioavailability of the therapeutic agents. The AD pathology is mostly mediated by the interplay of Aβ oligomers and oxidative stress as discussed earlier [48]. The nanotechnology-based approaches have been applied successfully to inhibit Aβ oligomerization as well as counteract oxidative damage; the findings of these applied studies for diagnosis and treatment of AD are already reviewed [80]. In this section, we highlight the recent development of the nanotechnology guided antioxidant therapy for AD.

4.3.1 Nanoparticles as antioxidants

The usage of two NPs, namely fullerence (C60) and cerium oxide (CeO2), has been tested as oxidative stress modulators for AD [81, 82]. Fullerence C60 prevents neurotoxicity by combining antioxidative as well as anti-Aβ aggregation properties [81]. The neuroprotective behavior of fullerenols (fullerene derivative) is because of both anti-oxidant reactions and inhibition of Aβ42-induced Ca2+ neurotoxicity [80]. Similarly, cerium oxide or nano-ceria has demonstrated neuroprotective effects in AD models due to its anti-oxidant properties [83, 84].

4.3.2 Nanocarriers for antioxidants

Curcumin can be used as a treatment for AD because of its antioxidant, anti-amyloidogenic, and anti-inflammatory properties [85]. However, it is quickly oxidized and hydrolyzed in the body before it can reach the brain. To overcome this problem poly n-butylcyanoacrylate (PnBCA) nanocapsules are used to carry it through the BBB. The PnBCA nanocapsules are covered by apolipoprotein E3 in order to use LDL receptors for passage through the BBB [80]. Another group of NPs called solid lipid nanoparticles (SLN) have been devised for the delivery of antioxidant agents to the brain. SLN has been safely used to carry a phenolic antioxidant derivative, ferulic acid [80]. The antioxidants can be present on the surface as shown or loaded into the nanoparticle core. The spacer molecule (polyethylene glycol or PEG) provides stability by improving pharmacokinetics of the nanoparticle and probe serves as a tracer molecule (e.g. fluorescent tag) when required.

Fig. 6. Representative antioxidant based nanocarrier. The surface of the nanoparticle is coated with targeting molecules such as peptides, aptamers, antibodies, and cationic molecules.

Fig. 7. Brain targeted delivery mechanisms for NP-based antioxidants across blood brain barrier (BBB).

5. CONCLUSIONS AND FUTURE DIRECTIONS

Oxidative stress plays a crucial role in a wide range of proliferative, degenerative, and metabolic diseases. The pathophysiologic association of oxidative stress and Alzheimer’s disease is well understood. Current lines of therapies for AD are scarce and unsatisfactory. These drugs,
instead of offering a cure, temporarily mitigate the clinical symptoms. The use of antioxidants as therapeutic agents for AD is very promising. But, most of the clinical trials with antioxidants failed to elicit desired anti-AD effects most likely due to inefficient delivery. Nanoparticles provide a possible solution to this, though. They are modifiable, effective drug/antioxidant delivery systems, and can target areas inaccessible to other delivery methods. Nonetheless, further advances are necessary in order to prevent or eliminate the onset of oxidative stress and associated neuropathogenesis. Future research in this field will open up new avenues not only for AD, but also for myriad of diseases where delivery of drugs as well as diagnostic and imaging agents requires passage through the blood brain barrier (BBB). This includes brain tumors as well as other neurodegenerative diseases like Parkinson’s disease (PD), Huntington’s disease, Amyotrophic lateral sclerosis (ALS) etc.

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References


