

A Hypothesis For The Green Synthesis Of Cerium Oxide Nanoparticles For Management Of Alzheimer Disease

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ABSTRACT

Alzheimer's Disease (AD), a widespread type of dementia, has a major effect on millions of people worldwide. Interestingly, with recent developments in nanotechnology such as the Nanodrug delivery method, which merits high specificity for brain endothelial cells, early detection of AD is probable. Due to its special radical scavenging feature, Cerium Oxide nanoparticles (CNP) were selected as a drug carrier in the present analysis, and CNP was synthesised by the Green synthesis process. The green synthesis of cerium oxide nanoparticles prepared was subjected to neuroprotective in vitro and in vivo assessment. The findings show that CNP 's Green synthesis is a promising and powerful formulation for AD. The CNP and anti-oxidant activity and free radical scavenging behaviour of the green synthesis of cerium oxide nanoparticles can be due to synergistic activity that enhances AD's neuroprotective and cognitive enhancement activity.

Keywords:

Cerium oxide nanoparticles (CNP), Reactive oxygen species (ROS), Synergism, Alzheimer's Disease (AD).

Introduction

Between 65 and 70 percent of instances of dementia are caused by Alzheimer's disease (AD), a neurodegenerative condition initially described by Alois Alzheimer. He was a German physician and a pathologist who discovered Alzheimer's disease in 1906. [1]. Bioaccumulative plaques and tangles in the brain may have an impact on a person's health. The exact aetiology of the clinical state and the symptoms of AD make it difficult to make a symptomatic diagnosis [2]. For such treatment neurological illnesses such as Alzheimer's, nanomedicine has the potential to revolutionise the treatment process by facilitating medication transfer past the Blood-Brain Barrier, which would be the primary disease-targeting barrier. The primary characteristics of nanotechnology drug transport [3] are a larger surface area and a higher bioavailability. Increased medicine permeability and reduced dose and duration of treatment due to nano-size formulation [4] enhance patient compliance [5]. Cerium oxide nanocerium (CNP), a drug including nanocarriers, has the extraordinary capacity to modify an oxidation state from +3 to +4, giving it an excellent treatment option for illnesses involving oxidative stress and inflammation, including such Alzheimer's disease (AD) [5]. In a great deal of research being used in-vitro models, nanocerium is one of the therapeutic active neuroprotective agents already mentioned, and experiments focused on ceramic oxides showed powerful antioxidant effects that resulted in neuroprotective effects. Owing to the lack of precise awareness of the biological cause for the disorder, AD is mainly symptomatic treatment in the present scenario. Current therapy does not successfully halt the progression of the disease, and a new approach to the management of the disease is now mandatory. It's also possible to employ nanocerium to provide an A (amyloid-beta) plaque treatment while simultaneously rescuing neuronal survival and preventing neurite degeneration using green nanoparticle manufacturing. It is believed that oxidative stress and is the primary pathogenic variables responsible for the activation of oxy free radicals in Alzheimer's disease (AD). This disorder may be treated using nanocerium because of its redox-active and biocompatible properties. There are two partly filled electron subshells (4f and 5d) but a valence structure that fluctuates greatly based on the chemical environment of the element, which makes it unusual in the lanthanide series. When cerium comes into contact with oxygen, it transforms into a cubic fluorite, which creates a surface that is extremely reactive and hence ideal for neutralising free radicals. Nanocerium's unique antioxidant effects may be attributed to its +3 oxidation condition. Oxygen moves quickly across the lattice [7]. Conflict of ferricytochrome C

in superoxide reduction increases as the valence gap widens[8]. Having Ce^{3+} in the centre of the oxygen vacancy is what makes CNP an aggregated fluorite lattice with oxygen that provides cellular protection. Oxygen has been found to protect cells by aggregating with it. In addition to their anti-oxidant properties, research shows that CNPs also aid in the regulation of signal transduction pathways important for neuroprotection[9]. Nanoceria showed neuroprotection against the harmful effects of A by altering intracellular signalling pathways having antioxidant capabilities, as described by D'Angelo et al., 2012[10]. There are many challenges to using Nanoceria, the most significant of which is that it quickly precipitates and aggregates, making it difficult to use in live formulations. In addition, its hydrophilic nature of the substance shows limited bioavailability and diffusion of tissues. In order to improve medication permeability across the blood-brain barrier and system stability, a hydrophilic nanoceria is an excellent choice for surface modification with Tripalmitin's lipidic NH group[11]. For the purpose of this investigation, cerium oxide nanoparticles were chosen because of their ability to inhibit the enzyme Acetyl Cholinesterase (AChE), as well as their ability to scavenge reactive oxygen species (ROS). In this research, we designed and characterised a new approach for brain-targeted administration for such therapeutic option of Alzheimer's disease via Green production of nanoceria.

Hypothesis

CeO₂ may scavenge free radicals by oxidation states of Ce^{+3} and Ce^{+4} in a continuous cycle and so have antioxidant properties. Toxic chemicals are often used in the manufacture of CeO₂ nanoparticles, making their biological uses more limited. Therefore the goal of this Research is to develop reliable non-toxic methods that are both environmentally friendly and efficient cerium oxide nanoparticles using microorganisms. Being a carrier and scavenger the developed nanoceria would be the dual targetting system for Alzheimer's disease.

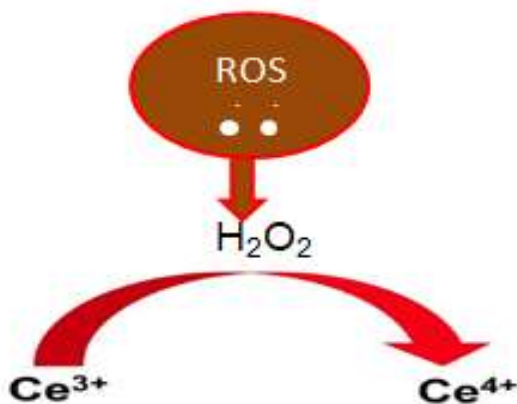


Figure :1 Schematic Diagram of possible role of cerium oxide as a antioxidant

Justification

Considering the current research status of AD, it is clear that field of Nanoceria via intranasal route of delivery is not well developed. Drugs used in the treatment of AD are limited mainly due to imbalance between drug discovery and drug delivery. Presently, marketed drugs provide only symptomatic relief which may be due to their inability to cross BBB, limited availability of drug delivery systems and side effects. Nanoceria is regarded a physiologically active antioxidant because of its redox nature. Nanoceria in combination with existing drugs rather than single drug treatment might be most beneficial for AD patients. Antioxidant and anti-inflammatory drugs have been investigated either alone or in combination with present marketed drugs. However, there has been little success since most of compounds cannot pass the blood-brain barrier. Since, intra-nasal route of drug delivery is a promising crossing the blood-brain barrier (BBB) non-invasively and delivering drugs directly to the brain is possible. A new method (green chemistry route) of Nanoceria has been developed. This novel nanocarrier improves drug loading and firmly incorporates the drug during storage. In chemistry and chemical technology, 'greener' environmentally sustainable methods are becoming increasingly common and are badly needed as a result of environmental pollution problems worldwide. So, there is an urgent need to develop non-toxic, biocompatible and biodegradable Nanoceria through green synthesis for effective management of AD.

Conclusion and Future Perspective

Antioxidant properties of the nanoceria might be advantageous in the treatment of neurodegenerative disorders like Alzheimer's disease, which are currently limited by the lack of effective treatment options. Scaling it up for more clinical research is feasible because to its therapeutic efficacy, stabilities, costs, non-toxicity, biocompatibility, and biodegradability. It's a green technology. An adequate amount of information on bio-directed new synthetic processes (green synthesis) and preclinical assessment of nanoceria's effectiveness and safety will be obtained via this research. The project has academic value because of the research papers it has produced, the conferences it has presented at, and the patents it has received. It has a direct influence on industry since the created nanoceria is proven, replicable, and standardised, which in turn gives rise to knowledge transfer and commercialization.

Conflict of Interest

The authors have no established conflicting financial interests

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References

1. Howard RJ, Juszczak E, Ballard CG, Bentham P, Brown RG, Bullock R, Burns AS, Holmes C, Jacoby R, Johnson T. Donepezil for the treatment of agitation in Alzheimer's disease. *N Engl J Med*. 2007;357:1382-92. DOI: 10.1056/NEJMoa066583
2. Raja Azalea D, Mohamed M, Joji S, Sankar C. Design and evaluation of chitosan nanoparticles as novel drug carriers for the delivery of donepezil. *Iranian Journal of Pharmaceutical Sciences*. 2012;8:155-64.

3. Umashankar M, Rini R, Aditi D, Kanchan K. Advancement of Nanopharmaceutics in Drug Delivery. SSN: 0976 822X
4. Berchtold NC, Cotman CW. Evolution in the conceptualization of dementia and Alzheimer's disease: Greco-Roman period to the 1960s. *Neurobiol Aging*. 1998;19:173-89. [https://doi.org/10.1016/S0197-4580\(98\)00052-9](https://doi.org/10.1016/S0197-4580(98)00052-9)
5. Wason MS, Colon J, Das S, Seal S, Turkson J, Zhao J, Baker CH. Sensitization of pancreatic cancer cells to radiation by cerium oxide nanoparticle-induced ROS production. *Nanomedicine: Nanotechnology, Biology and Medicine*. 2013;9:558-69. <https://doi.org/10.1016/j.nano.2012.10.010>
6. Nicolini V, Gambuzzi E, Malavasi G, Menabue L, Menziani MC, Lusvardi G, Pedone A, Benedetti F, Luches P, D'Addato S, Evidence of catalase mimetic activity in Ce³⁺/Ce⁴⁺ doped bioactive glasses, *The Journal of Physical Chemistry B*. 2015;119:4009-19. <https://doi.org/10.1021/jp511737b>
7. Ebrahimi M, Samadi M, Yousefzadeh S, Soltani M, Rahimi A, Chou T-c, Chen L-C, Chen K-H, Moshfegh AZ. Improved Solar-Driven Photocatalytic Activity of Hybrid Graphene Quantum Dots/ZnO Nanowires: A Direct Z-Scheme Mechanism. *ACS Sustainable Chemistry & Engineering*. 2016;5:367-75. <https://doi.org/10.1021/acssuschemeng.6b01738>
8. Li J, Fisher CL, Konecny R, Bashford D, Noodleman L. Density functional and electrostatic calculations of manganese superoxide dismutase active site complexes in protein environments. *Inorg Chem*. 1999;38:929-39. <https://doi.org/10.1021/ic980731o>
9. Zhou D, Fang T, Lu L-q, Yi L. Neuroprotective potential of cerium oxide nanoparticles for focal cerebral ischemic stroke. *Journal of Huazhong University of Science and Technology [Medical Sciences]*. 2016;36:480-6. DOI 10.1007/s11596-016-1612-9
10. Cimini A, D'Angelo B, Das S, Gentile R, Benedetti E, Singh V, Monaco AM, Santucci S, Seal S. Antibody-conjugated PEGylated cerium oxide nanoparticles for specific targeting of A β aggregates modulate neuronal survival pathways. *Acta Biomater*. 2012;8:2056-67. <https://doi.org/10.1016/j.actbio.2012.01.035>
11. Bhushan B, Khanadeev V, Khlebtsov B, Khlebtsov N, Gopinath P. Impact of albumin based approaches in nanomedicine: Imaging, targeting and drug delivery. *Adv Colloid Interface Sci*. 2017;246:13-39. <https://doi.org/10.1016/j.cis.2017.06.012>

12. Stöbel A, Schlenk M, Hinz S, Küppers P, Heer J, Gütschow M, Müller CE. Dual targeting of adenosine A_{2A} receptors and monoamine oxidase B by 4 H-3, 1-benzothiazin-4-ones. J Med Chem. 2013;56:4580-96. <https://doi.org/10.1021/jm400336x>