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Review

# Nano-antioxidants: An emerging strategy for intervention against neurodegenerative conditions

Rajat Sandhir [a, *], Aarti Yadav [a], Aditya Sunkaria [a], Nitin Singhal [b]

[a] Department of Biochemistry, Panjab University, Chandigarh 160014, India
[b] National Agri-Food Biotechnology Institute, Mohali 160071, Punjab, India

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ABSTRACT

Oxidative stress has for long been linked to the neuronal cell death in many neurodegenerative conditions. Conventional antioxidant therapies have been less effective in preventing neuronal damage caused by oxidative stress due to their inability to cross the blood brain barrier. Nanoparticle antioxidants constitute a new wave of antioxidant therapies for prevention and treatment of diseases involving oxidative stress. It is believed that nanoparticle antioxidants have strong and persistent interactions with biomolecules and would be more effective against free radical induced damage. Nanoantioxidants include inorganic nanoparticles possessing intrinsic antioxidant properties, nanoparticles functionalized with antioxidants or antioxidant enzymes to function as an antioxidant delivery system. Nanoparticles containing antioxidants have shown promise as high-performance therapeutic nanomedicine in attenuating oxidative stress with potential applications in treating and preventing neurodegenerative conditions. However, to realize the full potential of nanoantioxidants, negative aspects associated with the use of nanoparticles need to be overcome to validate their long term applications.



**Contents**



* Corresponding author.
*E-mail address:* sandhir@pu.ac.in (R. Sandhir).

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## 1. Introduction

The central nervous system (CNS) is highly vulnerable to oxidative stress because of low levels of antioxidant enzymes and high content of oxidant substrates (Morozova et al., 2007; Polidori et al., 2007). A promising neuroprotective strategy involves extenuating oxidative stress, which is a key player in various neurodegenerative disorders (Metodiewa and Koska, 2000). Antioxidants have received attention in recent years, due to their potential as prophylactic and therapeutic agents and more importantly their ability to fight oxidative stress. The main function of an antioxidant is to scavenge reactive oxygen species (ROS) and reactive nitrogen species (RNS) and convert them into less harmful or neutral products (Pellegrini et al., 2003). Since orally delivered antioxidants are easily destroyed by acids and enzymes, only a small portion of consumed antioxidant gets absorbed, leading to low bioavailability and low concentrations at the target site (Souto et al., 2013). Hence, there is an urgent need to develop effective methods for efficient delivery of antioxidants to the required sites. Efforts have been done towards loading antioxidant molecules in advanced nanoparticulate carriers, e.g., liposomes, polymeric nanoparticles (NPs), solid lipid NPs or self-emulsifying drug delivery system (Watal et al., 2013). Among the various nanoscale delivery mechanisms, nanoencapsulation has emerged as a key and an efficient delivery process which provides a protective vehicle that keeps the antioxidants from being destroyed in the human gut and ensures their better absorption. The blood brain barrier (BBB) is the homeostatic defense mechanism of the brain and hence affords barrier selectivity for the passage of drugs into the brain parenchyma (Modi et al., 2009). As carriers for drug delivery to the brain, NPs should be small (<100 nm) and stable in the blood, as well as escape the reticuloendothelial system (RES), neutrophil activation, platelet aggregation, and inflammation (Lockman et al., 2002). Some of recent studies focused on using nanomaterials having antioxidant properties to attenuate oxidative stress in the brain (Blass, 2003). Although, applications of nanotechnologies in clinical neuroscience are only in the early stages of development, the possibilities offered by using these nanomaterials for treatment of CNS disorders are outstanding. In this review nanoantioxidants employed in various neurodegenerative diseases have been discussed.

### 1.1. Evolution of nanoparticles

The origin of nanotechnology can be traced back to 1959 when physicist Richard Feynman (1960) recognized the potential of manipulating individual atoms and molecules at the nanometer scale and proposed that materials at this scale possess unique physical properties (Gilmore et al., 2008). As a separate discipline, nanoscience and nanotechnology emerged some 20 years ago (Suh et al., 2009). The NPs can be defined as particulate dispersions or solid particles with a size ranging from 10 to 1000 nm. The main motive of nanotechnology is the development and use of nanometer-scale materials known as NPs, which display unique functional properties not shown by bulk materials. The recent advent of different nanoscale materials in several key areas provides novel technological advances mainly in the field of medicine called nanomedicine.

Over the last decades, different types of NPs have been developed based on various components, including carbon, silica oxides, metal oxides, nanocrystals, lipids, polymers, dendrimers, and quantum dots, together with increasing variety of newly developed materials (Petros and DeSimone, 2010). Nanosize materials provide hope for a paradigm shift in drug delivery methods in near future. The drug can be dissolved, entrapped, encapsulated or attached to a matrix of NPs (Mohanraj and Chen, 2006). A number of surface modifications such as polyethylene glycol (PEG) addition, specific antibody conjugation, aptamer ligation, specific ligand binding, etc. on the nanosize makes them excellent delivery devices to selectively target a diseased cell thus avoiding the normal cell (Mukherjee, 2013). The first report on drug delivery using NP appeared in 1986 wherein solid colloidal drug delivery system was used for encapsulating pilocarpine for delivery to the eye (Harmia et al., 1986). Recent advancements in the field of nanotechnology hold the promise of developing targeted drug delivery systems. Over the next couple of years, it is widely anticipated that nanotechnology will continue to evolve and expand in many areas of life, and the achievements of nanotechnology will be applied to medical sciences, including diagnostics and drug delivery systems.

Due to the inherent ability of antioxidants to evoke free radical scavenging activity, their formulation as NPs will enhance their efficiency. The blending of material science with nanobiotechnology to reduce oxidative damage caused by free radicals in biological system with greater efficiency has been attained. The use of antioxidant NPs is likely to surpass all conventional antioxidant therapies resulting in improved quality of life and increased lifespan (Narayanan and Park, 2013).

### 1.2. Nanoparticle preparation

NPs can be prepared from a variety of materials such as metal salts, proteins, polysaccharides and synthetic polymers. The selection of matrix materials depends on many factors, including: (a) size of NPs required; (b) inherent properties of the drug, e.g., aqueous solubility and stability; (c) surface characteristics such as charge and permeability; (d) degree of biodegradability, biocompatibility and toxicity; (e) desired drug release profile; and (f) antigenicity of the final product (Mohanraj and Chen, 2006). NPs have been prepared most frequently by three methods: (1) dispersion of preformed polymers; (2) polymerization of monomers; and (3) ionic gelation or coacervation of hydrophilic polymers. However, other methods such as supercritical fluid technology and particle replication in non-wetting templates (PRINT) have also been described in the literature for production of NPs. The latter was claimed to have absolute control of particle size, shape and composition, which could set an example for the future mass production of NPs at an industrial scale (Mohanraj and Chen, 2006). The first nano-biotechnology approach reported is the cross-linking of hemoglobin to the ultrathin (nanodimension) membrane of crosslinked protein, which is used to form the membrane of artificial red blood cells (RBC). The advantage of artificial RBC is that it could be transfused without cross-matching, because they are devoid of blood group antigens (Chang, 2010).

### 1.3. Features of nanoparticles

During the past ten years many advancements in nanobiotechnology have been reported. A number of NP-based products for diagnostics and therapeutics have been approved for clinical applications (Bao et al., 2013). The properties and functions of some successful nanoantioxidants are mentioned in Box 1 (Couvreur, 2012; De Jong and Borm, 2008). NPs have attracted attention of biomedical scientists due to their ability to be administered by a variety of routes, including oral, intranasal, and parenteral (Petkar et al., 2011). Further, the large surface-area-to-volume ratio of NPs permits multiple copies of a ligand to be attached and thereby dramatically increase their binding affinity via the multivalent functionalization (Montet et al., 2006).