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Review article

# Free radicals and polyphenols: The redox chemistry of neurodegenerative diseases

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ABSTRACT

The oxidation of bioorganic materials by air and, particularly, the oxidative stress involved in the cell loss and other pathologies associated with neurodegenerative diseases (NDs) are of enormous social and economic importance. NDs generally involve free radical reactions, beginning with the formation of an initiating radical by some redox, thermal or photochemical process, causing nucleic acid, protein and lipid oxidations and the production of harmful oxidative products. Physically, persons afflicted by NDs suffer progressive loss of memory and thinking ability, mood swings, personality changes, and loss of independence. Therefore, the development of antioxidant strategies to retard or minimize the oxidative degradation of bioorganic materials has been, and still is, of paramount importance. While we are aware of the importance of investigating the biological and medical aspects of the diseases, elucidation of the associated chemistry is crucial to understanding their progression, heading to intelligent chemical intervention to find more efficient therapies to prevent or delay the onset of the diseases. Accordingly, this review aims to provide the reader with a chemical base to understand the behavior and properties of the reactive oxygen species involved and of typical radical scavengers such as polyphenolic antioxidants. Some discussion on the structures of the various species, their formation, chemical reactivities and lifetimes is included. The ultimate goal is to understand how, when and where they form, how far they travel prior to react, which molecules are their targets, and how we can, eventually, control their activity to minimize their impact by means of chemical methods. Recent strategies explore chemical modifications of the hydrophobicity of potent, natural antioxidants to improve their efficiency by fine-tuning their concentrations at the reaction site.



**Contents**



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## 1. Introduction

Neurodegenerative disorders are a heterogeneous group of diseases of the nervous system, including the brain, spinal cord, and peripheral nerves that have different etiologies [1–3]. The diseases are characterized by degradation of regions of the brain as consequence of hereditary, toxic, metabolic or infectious processes and represent significant medical, social, and financial burden on the society due to their prevalence, morbidity, and mortality. Table 1 summarizes some clinical features of the major neurodegenerative diseases [4–7]. The exact mechanism of NDs development is still not clear in spite of the increased current knowledge of their neurobiology. However, there is consensus in recognizing that the oxidative stress - an imbalance caused by an overproduction of free radicals - is closely associated with the development of NDs and leads to severe molecular damage in cell components such as protein oxidation, lipid oxidation, DNA oxidation, and glycoxidation [8–11].

Aerobic life is characterized by a continuous production of free radicals such as reactive oxygen and nitrogen species (ROS and RNS, respectively), which are generated under physiological conditions in normal metabolism as part of several physiologic processes including signal transduction pathways [12]. ROS play a dual role as both deleterious and beneficial species [12,13]. Beneficial effects of ROS occur at low/moderate concentrations and include cellular responses to noxia (e.g., defense against infectious agents), cellular signaling, and induction of mitogenic responses [9,14,15]. The harmful effects of free radicals causing potential biological damage are a consequence of their overproduction as a result of an increase in ROS production, a decrease in antioxidant defense or an excess of prooxidants (e.g. metal ions) [10,12,16,17]. ROS and other species derived from radicals operate at low, but measurable concentrations in the cells. Each cell is characterized by a particular concentration of oxidants and antioxidants (AOs), and the balance between the rates of production of ROS and the rates of removal (for instance, by antioxidant scavenging processes) determines their “steady state” concentrations [10,18]. The redox state of a cell and its oscillation determines cellular functioning and is usually kept within a narrow range under normal conditions—similar to the manner in which a biological system regulates its pH [10]. When, for any reason, there is an imbalance between the production of ROS and the cellular defense system responsible for the removal of ROS, formation of toxic substances is possible promoting the development of NDs [14,15,19].

This delicate balance between beneficial and harmful effects of free radicals results from the metabolic reactions that use oxygen and constitute a very important aspect of protecting living organisms and maintaining the “redox homeostasis” by controlling the redox regulation *in vivo* [19]. It is not surprising, therefore, that, because of the affinity of ROS for lipids, proteins and DNA, the role of free radical reactions in neurodegenerative human diseases, in biology, toxicology and in food deterioration has become an area of interest for years [11,14,15,20].

Polyphenolic antioxidants have been used for centuries in preventive medicine, and human epidemiological studies support the idea that there is an inverse relationship between antioxidant levels and intake and cognition function and development of NDs [21,22]. Polyphenols constitute one of the most important groups of secondary metabolites of plants. They are widely distributed in the plant kingdom and can be obtained directly from plants and other antioxidant-rich foods or drug-supplements, gaining the attention worldwide as nutraceuticals in the prevention of several diseases [23]. The health benefits and anticancer effects linked to the regular consumption of these polyphenol-rich foods made that the intake of exogenous antioxidants such as polyphenols and vitamins (e.g., vitamin C, E) to be an effective therapy to keep our health against ROS and antioxidant strategies for the treatment of NDs, particularly Alzheimer disease (AD) have advanced in the last decade [24–30].

Polyphenols function as antioxidants because they are excellent hydrogen donors that are accepted by reactive radical to yield much less reactive radical and non-radical species [31]. A careful choice of the physicochemical characteristics of polyphenols is crucial because strongly affects their bioavailability and chemical reactivity

**Table 1**
Main characteristic features of some common neurodegenerative diseases.

| Neurodegenerative disease | Clinical features | Neuropathology |
|---|---|---|
| Alzheimer's disease (AD) | Dementia, deterioration of language skills, perception | Senile plaque, extracellular deposit of beta-amyloid |
| Amyotrophic lateral sclerosis (ALD) | Atrophy of skeletal muscles, progressive weakness | Loss of primary motor neurons in the neocortex |
| Parkinson's disease (PD) | Tremor, rigidity, slowness of movement, | Neuronal degeneration die to loss of pigmented neurons |
| Huntington's disease (HD) | Cognitive impairments (dementia), personality changes, depression | Atrophy of the stratium, generalized cortical atropy with decrease brain |