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Review article

# Berberine and neurodegeneration: A review of literature

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ABSTRACT

The excessive production of reactive oxygen species in nervous tissues is considered one of the major risk factors of neurodegenerative diseases. During the last two decades, much attention has been paid to the antioxidant and anti-inflammatory activity of natural products and compounds isolated from natural products which are often characterized by high efficacy and low adverse effects. Berberine is an isoquinoline alkaloid, widely present in different medicinal herbs, especially in the genus Berberis. It is mainly used as antidiarrhoeal, antibacterial, antifungal, and antiprotozoal agent. However, current research has focused on its beneficial role in neurodegenerative diseases, mainly due to its powerful antioxidant effect. The therapeutic potential of Berberine in different neurodegenerative diseases such as Alzheimer, Parkinson and Huntington disease has been brought to evidence by numerous studies. However, a limited number of reviews focus on the beneficial role of Berberine against neurodegeneration. The main objective of this review is to discuss the role of oxidative stress in neurodegeneration and the potential role of antioxidant compounds, in particular Berberine which is analyzed in its chemical structure, source, bioavailability, therapeutic potential, with special attention to its mechanism of action at a molecular level.



**Contents**



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## Neurodegeneration and oxidative stress

The excessive production of free radical species (ROS) plays a central role in oxidative stress and cellular damage for the human body [1–3]. During oxidative stress, ROS cause lipid peroxidation and protein oxidation, resulting in plasma membrane damage as well as cross-linking of cytoskeletal biomolecules [4,5]. ROS can also cause oxidative damage to nucleobases and sugar moieties of RNA and DNA [6]. The nervous tissue is very susceptible to oxidative damage due to multiple reasons, such as: high metabolic activity, low levels of non-enzymatic antioxidants (glutathione) and antioxidant enzymes (superoxide dismutase (SOD), catalase, and glutathione peroxidase) and to high levels of polyunsaturated fatty acid [7,8]. In addition, a selective regional susceptibility for neurodegeneration and oxidative damages in the nervous tissue has been reported [9]. For example, Parkinson disease shows high susceptibility to neurodegenerative decline borne by the dopaminergic neurons of the substantia nigra, whereas in amyotrophic lateral sclerosis (ALS) are involved the motor neurons of the spinal cord and in Alzheimer disease the cholinergic neurons in the basal forebrain are selectively lost [10,11].

It has been reported that several environmental toxins such as paraquat, rotenone, and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine can generate reactive oxygen and nitrogen species directly through the alkylation of reduced thiols, inhibition of complex I of the mitochondrial transport chain, activation of microglia, as well as induction of α-synuclein aggregation in the neuronal tissues. In addition, they can alter metal homeostasis together with dopamine metabolism and increase the levels of non-vesicle-associated dopamine [12]. Reactive oxygen and nitrogen species responsible for cell death are thus generated. To date, there are several scientific evidences regarding other molecular pathways which have important roles in the pathophysiology of Parkinson's disease, such as membrane NADPH oxidases, cytosolic flavoproteins and nitric oxide (as an important contributors of protein dysfunction and cell death) [12]. Despite the unknown pathophysiology of ALS, oxidative stress has a crucial role in both the onset and progression of this disease [13,14]. There is scientific evidence that different molecular pathways are involved in the pathophysiology of ALS, such as mutation on SOD1, glutamate excitotoxicity, different protein misfolding, mitochondrial dysfunction, upregulation in the expression of different cytokines, as well as cyclooxygenase-2 and matrix metalloproteinases [15–22]. In addition, there is also scientific evidence that ALS progression is associated with skeletal muscle dysfunction, calcium toxicity and autoimmune response [23–26].

Numerous scientific reports underline the importance of oxidative stress in the pathophysiology of Alzheimer's disease [27–29]. The percentage of iron is higher in neurofibrillary tangles and amyloid beta [30,31]. It is well known that iron catalyzes the production of the hydroxyl radical and of advanced glycation end-products [32,33]. It has been also reported that in the presence of transition metals, advanced glycation end-products promote redox cycling and generate reactive oxygen species [33]. Moreover, the accumulation of aluminum in the neurofibrillary tangles triggers iron-induced oxidative stress and lipid peroxidation [34]. Furthermore, it is well known that activated microglia are another important source of nitric oxide and superoxide anion radicals which can easily react to produce peroxynitrite [35]. Amyloid beta plays an important role in the production of reactive oxygen species through peptidyl radicals [36], as a matter of fact it can activate some receptors such as that for advanced glycation end products as well as the class A scavenger-receptor thus increasing the production of free radicals [33,37].

For all the reasons above mentioned, oxidative stress plays a crucial role in the onset and progression of neurodegeneration [38,39]. In such a pathological condition, ROS cause lipid peroxidation by increasing F2-isoprostanes in the nervous tissue [12]. Moreover, oxidative stress increases the levels of protein oxidation (protein carbonyls) and damages the DNA [40]. Over the last years special attention has been paid to the use of antioxidant compounds against neurodegenerative diseases [41].

## Therapeutic potential of antioxidants in neurodegeneration

There is an inverse correlation between a high consumption of vitamin E and the incidence rate of Parkinson's disease [42,43]. Similarly, vitamin C has shown its benefits in Parkinson's disease [43]. In addition, clinical studies have demonstrated that dietary antioxidants reduce the incidence rate of neurodegenerative diseases [44,45]. Literature confirms that a diet rich in fruits and vegetables such as blueberries, strawberries and spinach which contain flavonoids and natural antioxidants, reduces oxidative stress and cognitive dysfunctions in animal models of neurodegeneration [46–48]. These findings strongly suggest that the intake of antioxidants in our daily diet might mitigate oxidative stress and reduce the risk of neurodegeneration.

Recent evidence from epidemiological studies showed that dietary pattern affects the incidence rate of neurodegenerative disorders [49]. One cohort study has indicated that there is a close correlation between wine consumption and the risk of neurodegeneration [50], showing that those subjects who drink wine are significantly less likely to develop neurodegenerative disorders compared to those who do not drink wine [50]. Another study reported that wine consumption shows protective effect against Alzheimer-like induced insult [51]. This beneficial role could be due to the high amount of antioxidant compounds such as polyphenols which can increase the activity of antioxidant enzymes as well as non-enzymatic antioxidants [50,52–57]. Numerous side-effects are associated with synthetic antioxidants therapy such as liver damage, carcinogenesis, *etc*. Therefore, much attention has been paid to find natural antioxidants as an effective therapeutic strategy to combat oxidative stress-related diseases [58–61]. During the last couple of decades a plethora of studies have been carried out leading to an upsurge in finding several natural products with effective antioxidant properties [62–67].

## Antioxidant properties of Berberine

Berberine is known to have a wide range of biological activities such as antioxidant, antibacterial, antifungal, antiviral, anti-inflammatory, anti-tumor, antidiarrhoeal, antidyslipidemic and antidiabetic [68–74].

Berberine quenches superoxide anions and nitric oxide and exerts radical scavenging activity against the high reactive peroxynitrite and hydroxyl radicals [75]. In addition to its high free radical scavenging effects, Berberine shows strong $Fe^{2+}$ chelating activity [76]. In cell based systems, Berberine inhibits ROS production [77]. It prevents NADPH oxidase mediated generation of superoxide anions in the lipopolysaccharide stimulated human monocyte-derived macrophages [78]. It has been also reported that Berberine inhibits NO production lipopolysaccharide stimulated murine macrophages by inhibiting iNOS expression [37]. In addition, numerous reports showed that Berberine induces antioxidant defenses by increasing the levels of non-enzymatic antioxidants [79,80]. Furthermore, Berberine inhibits the reduction of glutathione, vitamin C and vitamin E in the azoxymethane-induced carcinogenicity in rats thus diminishing the level of lipid peroxide and preventing malignant morphological changes, as well as decreasing the apoptosis of goblet cells in experimental animals [81]. In addition, Berberine increases the activity of antioxidant enzymes both *in vitro* and *in*