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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*

vivo [81–83]. For example, it increases the activity of SOD in lipopolysaccharide stimulated murine macrophages and it reduces the intracellular superoxide anions [84]. It modifies the activity of SOD in hydrogen peroxide-treated rabbit corpus cavernosum smooth muscle cells, reduces the level of lipid peroxides and maintains the level of nitric oxide [83]. In addition, Berberine significantly maintains the activity of antioxidant enzymes such as SOD, catalase, glutathione peroxidase, as well as glutathione S-transferase in azoxymethane-induced carcinogenic rats [81]. Another study showed that Berberine restores the activity of SOD in rats with type 1 diabetes mellitus [85]. In severely immunodeficient rats, Berberine reduces the level of superoxide anions, nitric oxide and peroxynitrite and restores the activity of superoxide dismutase, catalase and glutathione peroxidase [84]. Berberine is believed to act as a double edge sword; an antioxidant in normal cells and a pro-oxidant in carcinogenic cells. In cancer cells, Berberine initiates oxidative stress and favors an apoptotic effect [86], but it also has an anti-apoptotic effect in normal cells [87]. It seems that pro-oxidant effects of Berberine play an important role in the endoplasmic reticulum stress initiation and also in the caspase-dependent apoptosis [88].

Traditional usages

The genus *Berberis* plants belong to the *Berberidaceae* family and comprise approximately 450–500 species of deciduous and evergreen plants representing its main source which is also extracted from *Hydrastis canadensis* (Goldenseal), used against inflammation, infections, diabetes and constipation [89]

In traditional Chinese medicine, Berberine has been widely used as antimicrobial, antiprotozoal, and anti-infective agent for different fungal, yeast, parasites and viral infections [90,91]. It has been used as a drug against *methycillin-resistant Staphylococcus aureus* (MRSA) for over 2000 years in China [92], very popular for its medicinal use in treating diarrhea and intestinal parasites, particularly in the far-East, and known to act through multiple pathways [93,94]. Interestingly, there are numerous reports about its antimicrobial and antiprotozoal activities against different types of infectious organisms [95–97]. Chinese people used it for treating diabetes [98]. Sometimes a dietary supplement for relieving a fever, common cold, respiratory infections as well as influenza [99], Berberine has been also used as astringent to tone down the skin and has beneficial effects on the upper airways, the gastrointestinal system, the bladder and the rectum [100,101].

Berberine chemistry

The chemical structure of Berberine (5,6-dihydrodibenzo[a,g] quinolizinium derivative) (Fig. 1) is an important chemical skeleton in medicinal chemistry. In fact, it is known as a natural lead structure for the discovery of different bioactive derivatives through the modification and substitution of functional groups in appropriate positions for designing selective and powerful bioactive molecules [102]. Berberine, a well known chemical derivative of 5,6-dihydrodibenzo [a,g] quinolizinium [103]. The sensitivity of the polar C=N$^+$ bond to a nucleophilic bond is the main characteristic of these iminium salts which leads to the formation of adducts with a substituted C-8 position [103]. Therefore, 8-substituted-7,8-dihydroBerberines are generated through the reaction of Berberine with the Grignard reagent RMgX (X=Br or I) [103]. The 8-substituted-7,8-dihydroBerberines is transformed through halogen oxidation and produces 8-substituted Berberines [102]. The modification of the C-13 position represents another method for incorporating a carbon atom inside the chemical structure of Berberine [103]. Therefore, 13-substituted derivatives

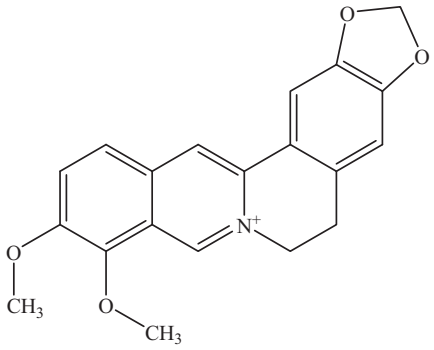

Fig. 1. Chemical structure of Berberine.

of Berberine are produced by using enamine 8-acetonyl-7,8-dihydroBerberine in a two-step reaction obtained through the nucleophilic attack of acetone to the iminium moiety in the Berberine skeleton followed by the loss of acetone through C-alkylation with electrophiles consequent to 13-substituted Berberine [103,104]. Another strategy used for the synthesis of 13-substituted Berberine is represented by a three-step reaction from the 7,8-dihydroBerberine which produces iminium intermediate by C-alkylation of 7,8-dihydroBerberine with electrophiles, then reduced to produce tetrahydroBerberine [103,105]. Eventually, 13-substituted Berberine is synthesized following an halogen oxidation of tetrahydroBerberine [102,105].

Sources and bioavailability

The genus *Berberis* is known as the most popular eatable herbal source of Berberine. The bark of *Berberis vulgaris* contains more than 8% of alkaloids, among which Berberine is the major alkaloid (close to 5%) [106]. Berberine is also largely found in leaves, twigs, roots, rhizomes, stem, and barks of different medicinal plants species such as, *Argemone mexicana*, *Berberis aristata*, *Berberis aquifolium*, *Berberis heterophylla*, *Berberis beaniana*, *Coptis chinensis*, *Coptis japonica*, *Coptis rhizome*, *Hydrastis canadensis*, *Phellodendron amurense*, *Phellodendron chinense Schneid*, *Tinospora cordifolia*, *Xanthorhiza simplicissima* [101,107–114]. However, roots and bark are richer in Berberine compared to other parts [115]. *Berberis croatica* is reported as a novel source of Berberine [116]. *Chelidonium majus* from the *Papaveraceae* family is another herbal source of Berberine in nature [117].

Despite its wide distribution in multiple herbs with a wide range of medicinal effects, Berberine is poorly absorbed by the intestine. However, it has been reported that D-α-Tocopherol polyethylene glycol 1000 succinate can be an effective method for increasing its intestinal absorption [118]. In addition, Berberine is a substrate component of P-glycoprotein and it is well known that P-glycoprotein plays a crucial role in the absorption of Berberine [119].

A plethora of scientific evidences showed that Berberine is metabolized through demethylation, glucuronidation and/or sulfation. Berberine can pass the blood-brain barrier and it can be detected in CSF followed by slow elimination. Therefore, it can directly affect brain tissues and accumulate in rats' hippocampus after intravenous administration. Wang et al. [120] examined the kinetic characteristics of Berberine after intravenous administration in rats. They report some pharmacokinetic parameters of Berberine including: half-life, 0.22 h, maximum thalamus concentration, 272 ng/g, time to peak concentration, 3.67 h and elimination half-life, 12.0 h.

Completed and ongoing clinical trials

Given its relatively safe nature and its numerous pharmacological actions, Berberine has a beneficial role in the treatment of human diseases [89,121,122]. A search in http://www.clinicaltrials.gov showed that there are 17 clinical trials on the efficacy of Berberine for a wide range of diseases including hyperlipemia, polycystic ovary syndrome, non-alcoholic fatty liver, type-2 diabetes mellitus, prediabetes, obesity, and coronary artery disease. There are seven completed clinical trials on the clinical efficacy of Berberine, mainly related to the metabolic syndrome. Only one completed clinical trial is on non-alcoholic fatty liver. Table 1 summarizes completed clinical trials on Berberine.

Berberine side effects

Though, there is very limited evidence reporting the adverse effects of Berberine, but some important studies are discussed here. Berberine treatment at the dose of 5–15 mg/kg decreased the number of dopaminergic neurons in the substantia nigra and the striatum [123]. This suggests that the Berberine has some toxic effect on these neurons and these adverse effects might results in disturbances in the motors and cognitive functions. Furthermore, the Berberine has shown in the cell culture system that Berberine inhibits the dopamine synthesis [124], and found to be neurotoxic (at the dose of 10–30 μM) by enhancing neurotoxicity of 6-hydroxydopamine. In future, specific studies are required which should address the point that what is the toxic dose of Berberine when given alone and how long treatment is toxic and interactions with other chemicals, so that the pharmacological profile of the Berberine can be evaluated while looking at its different activities. Recently it was found that micromolar concentrations of Berberine cause mitochondria-dependent toxicity in cultured primary neurons [125], and this toxic effect was rescued by blocking NMDA receptors [125]. Berberine was also found to sensitize neurons to the glutamate excitotoxicity [125]. Knowing the fact that penetration of Berberine into the nervous system is high, these adverse effects can be harmful for the human beings. Finally there is also one report which suggests that Berberine can induce DNA damage [126]. To provide conclusive evidence about the toxicity of the Berberine, there is a strong need to have more studies which should explore for potential Berberine toxic effects in multiple systems.

Berberine and neurodegeneration

Berberine has been extensively studied for its therapeutic efficacy against neurodegeneration and is likely to be a potential candidate to rescue neurodegeneration in various situations. Its ability to inhibit the activity of the most important pathogenic enzymes in Alzheimer's disease is as well reported [127].

As regards *in vitro* studies, Berberine protects neuronal cells in different *in vitro* models of neurotoxicity including glutamate, hydrogen peroxide, oxygen-glucose deprivation, N-methyl-D-aspartate (NMDA)-type glutamate receptor stimulation as well as $CoCl_2$-induced hypoxia.

Berberine is reported to stop glutamate-induced toxicity, such as protein mis-folding, aggregation, mitochondrial fragmentation and neurodegeneration in astroglial cells cultures system [128]. Kwon et al. reported that a treatment with Berberine increases cytotoxicity of 6-hydroxydopamine in PC12 cells which leads to degeneration of dopaminergic neurons in the substantia nigra of rats. They concluded that long-term L-DOPA therapy along with Berberine administration may be associated with side effects [129]. Therefore, further studies are required to understand such effects produced by Berberine. The promising effect of Berberine on oxygen–glucose deprivation-induced neurotoxicity in PC12 cells has been previously reported [130]. Zhou et al. [130] with their study showed that Berberine administration inhibits oxygen-glucose deprivation-induced intracellular reactive oxygen species generation and subsequently suppresses cytochrome c together with the release of apoptosis-inducing factors suggesting its therapeutic significance in the stroke management.

Table 1
List of completed clinical trials.

Number	Title	Main results	References
NCT00633282	Role of pioglitazone and Berberine in treatment of non-alcoholic fatty liver disease	Serum cholesterol (29%), triglycerides (35%) and LDL-cholesterol (25%) have been decreased after treatment.	[156]
NCT00462046	Efficacy and safety of Berberine in the treatment of diabetes with dyslipidemia	Treatment with Berberine decreased fasting plasma glucose (from 7.0 ± 0.8 to 5.6 ± 0.9 mm/liter), postload plasma glucose (from 12.0 ± 2.7 to 8.9 ± 2.8 mm/liter), HbA1c (from 7.5 ± 1.0% to 6.6 ± 0.7%), triglyceride (from 2.51 ± 2.04 to 1.61 ± 1.10 mm/liter), total cholesterol (5.31 ± 0.98 to 4.35 ± 0.96 mm/liter), low-density lipoprotein-cholesterol (from 3.23 ± 0.81 to 2.55 ± 0.77 mm/liter). The rate of glucose disposal has been increased after treatment with Berberine.	[157]
NCT00425009	Therapeutic effects of Berberine in patients with type 2 diabetes	Berberine treatment decreased hemoglobin A1c (from 9.5 ± 0.5% to 7.5 ± 0.4%), fasting blood glucose (from 10.6 ± 0.9 mmol/L to 6.9 ± 0.5 mmol/L), postprandial blood glucose (from 19.8 ± 1.7 to 11.1 ± 0.9 mmol/L) and plasma triglycerides (1.13 ± 0.13 mmol/L to 0.89 ± 0.03 mmol/L)	[158]
NCT02078167	Long term efficacy and tolerability of a nutraceutical combination (red yeast rice, policosanols and Berberine) in low-moderate risk hypercholesterolemic patients: a double-blind, placebo controlled study	Treatment with nutraceutical combination decreased total cholesterol (−30.3 ± 33.9%) and LDL-C at week 4 (−29.4 ± 35.3%). No significant effects have been observed on the serum levels of HDL-C, fasting glucose, and triglyceride in either group	[159]
NCT01562080	Combined effects of bioactive compounds in lipid profile (arm-plus-ldl)	Treatment decreased the levels of LDL-c, total cholesterol/HDL-c and also ApoB/ApoA1 ratios and increased Apo A1	[160]
NCT01087632	Armolipid plus and metabolic syndrome	Treatment decreased the homeostasis model assessment of insulin resistance index, low density lipoprotein cholesterol, blood glucose and insulin as well as in arterial systolic blood pressure and increased in flow-mediated dilation	[161]
NCT00654459	Effects of armolipid plus on cholesterol levels and endothelial function		

Berberine attenuated hydrogen peroxide-induced neurotoxicity through the activation of PI3k/Akt/Nrf-2 dependent pathway and it showed protective effect on SH-SY5Y cells neurites through the inhibition of ROS and apoptosis [131]. Berberine also enhanced NGF expression and promoted neurite outgrowth, suggesting its multifaceted roles in neuroregenerative processes [131].

Similar studies performed by Chai et al. [132] showed that Berberine administration to PC12 cells and primary neurons inhibits oxygen-glucose deprivation-induced neurotoxicity through the downregulation of p53, cyclin D1 and caspase-3, and the upregulation of Bad phosphorylation. They found that the activation of PI3 K/Akt pathway by Berberine plays an important role in its neuroprotection activity against ischemic stroke [132].

Similarly, Cui et al. [133] study showed that Berberine administration in mouse organotypic hippocampal slice cultures ameliorates oxygen and glucose deprivation and N-methyl-D-aspartate (NMDA)-type glutamate receptor stimulation-induced ischemic neuronal damages. They found that Berberine ability to suppress Bcl-2 phosphorylation plays a pivotal role in its neuroprotective effect against ischemic damages [133].

Zhang et al. [134] studied the anti-apoptotic effect of Berberine on CoCl2-induced hypoxia in PC12 cells. They found that downregulation of hypoxia-inducible factor 1, caspase 9 and 3 and Bax as well as upregulation of Bcl-2 are the main molecular mechanisms involved in anti-apoptosis [134]. Hsu et al. [135] investigated the possible protective effect of Berberine on hydrogen peroxide-induced NSC34 motor neuron-like cells damages. They found that the administration of Berberine in nanomolar concentrations increases cell survival by suppressing oxidative stress, downregulating cytochrome c, Bax and caspase, upregulating nuclear factor (erythroid-derived 2)-related factor-2 (Nrf2)/heme oxygenase (HO)-1, endogenous antioxidants (GSH and SOD), and antiapoptotic protein Bcl-2 and enhancing the mitochondrial function. They concluded that PI3K/AKT dependent mechanism has a pivotal role as a neuroprotector against hydrogen peroxide induced neuronal damages [135].

Wang et al. [136] evaluated the effect of Berberine administration on potassium currents in acutely isolated CA1 pyramidal neurons of rat hippocampus. They found that Berberine administration can block K^+ currents showing this way a neuroprotective effect against ischemic stroke [136]. Similar effects have been reported from its metabolite form, tetrahydroBerberine, on potassium currents in acutely isolated CA1 pyramidal neurons of rat hippocampus [137,138]. Wu et al. [139] studied the promising effect of tetrahydroBerberine administration on dissociated dopaminergic neuron degeneration from the substantia nigra pars compacta of rats. They found that tetrahydroBerberine administration exerts its neuroprotective effect and ameliorates rotenone-induced membrane hyperpolarization through the blockage of neuronal ATP-sensitive potassium channels in substantia nigra pars compacta dopaminergic neurons [139]. Wu et al. [140] used immunohistochemistry, neuronal culture and patch clamp technique to determine possible anti-apoptosis mechanism of tetrohydroBerberine against beta-amyloid peptide induced apoptosis. He found that a decreased hippocampal neuronal intracellular free Ca^{2+} is the main ionic anti-apoptotic mechanism of tetrohydroBerberine [140].

As regards animal studies, neuroprotective effect of Berberine have been shown in different experimental model, including a rat model of amyloid beta induced-Alzheimer's disease, aluminum-induced neurodegeneration, MPTP and 6-hydroxydopamine-induced Parkinson's disease in rats, stroke induced by middle cerebral artery occlusion in mice and rats, sciatic nerve injury in rats, Scopolamine and streptozotocin-induced memory impairment in rats, MK-801-induced neurodegeneration in rats, transient forebrain ischemia in gerbils, nicotine-induced behavioral sensitization in rats, mice model of autoimmune encephalomyelitis, and transgenic mouse mode of Alzheimer's disease.

A 12 week treatment with Berberine has shown reduction in superoxide dismutase and cholineacetyl transferase in rat models of aluminum-induced neurodegeneration. Moreover, Berberine decreased MDA contents and all these effects additively resulted in the rescuing effect of Berberine in aluminum-induced neurodegeneration [141]. Literature has also shown that Berberine suppresses pathological glutamate release from rat cortical synaptosomes *via* the downregulation of presynaptic Cav2.1 channels and ERK/synapsin signaling, thus, highlighting the therapeutic potential of Berberine in a wide range of neurological disorders requiring glutamate modulation [142]. Berberine is known to enhance motor balance by specifically preventing dopaminergic neural damage [129]. It also inhibited hippocampal apoptosis and dopaminergic neuronal damage thanks to its antioxidant activities in MPTP-induced Parkinson's model and the maximal effect was observed at the dose of 50 mg/kg [129]. There are a couple of reports showing that 5–15 mg/kg of Berberine caused degeneration of the dopaminergic neurons in the substantia nigra, underlining its side effects [123,124]. Shin et al. examined the effects of Berberine on long-term L-DOPA therapy in 6-hydroxydopamine-induced Parkinson's disease in rats. They found out that a treatment with Berberine causes degeneration of dopaminergic neurons in the substantia nigra of rats with long-term L-DOPA therapy [123,124]. A report suggests that mice suffering from ischemic stroke induced by middle cerebral artery occlusion and treated with Berberine resulted in reduced ischemia-induced cerebral infarction, and the underlying mechanism was attributed to the inhibition of reactive oxygen species and to a pro-apoptotic effect [130]. Berberine is also known to promote the survival of hippocampal precursor cells while in the peripheral nervous system, Berberine showed neuroregenerative effect and the axonal remyelination of nerve injury models in rats [143].

Zhu and Qian [144] studied the possible effect of Berberine chloride administration on spatial memory and inflammation in a rat model of Alzheimer's disease. They found that two week intragastric administration of 50 mg/kg Berberine chloride ameliorates memory impairment and exaggerates inducible nitric oxide and interleukin 1beta expression in the hippocampus of rats suffering from amyloid beta-induced Alzheimer's disease. The promising effect of Berberine administration on neuronal impairment and memory dysfunction is also studied in scopolamine-induced memory deficit in rats [145]. A 2 week administration of 20 mg/kg of Berberine significantly enhances memory impairment by stimulating the cholinergic enzyme activity, restoring brain-derived neurotrophic factor and cAMP-response element-binding protein mRNA expression as well as the downregulation of proinflammatory cytokines expression in rats hippocampus [145]. Similarly the promising effect of one month treatment with Berberine (25–100 mg/kg p.o. twice daily) on streptozotocin-induced memory impairment in rats has been previously reported [146]. Bhutada et al. [146] showed that Berberine administration significantly suppresses oxidative stress, hyperglycemia and cholinesterase activity and, consequently, it enhances memory function in diabetic rats. A similar study performed by Kalalian-Moghaddam et al. [147] showed that the treatment with Berberine ameliorates streptozotocin-induced memory impairment through the downregulation of pyramidal neurons apoptosis in hippocampal CA1 and it enhances the hippocampal synaptic plasticity.

Lee et al. [148] studied the neuroprotective effect of Berberine in MK-801-induced neurodegeneration in the rat brain. They found that Berberine administration protected neuronal cell by enhancing the activity-dependent cell survival mediated by NMDA receptor [148]. Similarly Yoo et al. [149] found that the

administration of barberry extract (rich source of Berberine) has neuroprotective effects in gerbil hippocampal CA1 region after transient forebrain ischemic stroke through the downregulation of N-methyl-D-aspartate receptor type 1 [149]. The same author [150] reported that the extract of *Berberis koreana* given to gerbils suffering from transient ischemic stroke, downregulates cyclooxygenase-2 expression and prostaglandin E2 production in the animal hippocampal CA1 region after transient ischemic stroke. They concluded that the anti-inflammatory effect of *B. koreana* extract plays an important therapeutic role against ischemic stroke [150].

Previous studies underlined that a treatment with *Coptidis Rhizoma* extract or its main alkaloid Berberine, significantly enhanced nicotine-induced behavioral sensitization and downregulated *c-fos* (early markers of neurotoxicity) expression in dopaminergic area of rats' brain [151]. The administration of Berberine significantly suppresses glutamate release from rats cortical synaptosomes and shows a neuroprotective effect mediated by the inhibition of presynaptic Cav2.1 channels as well as the downregulation of extracellular signal-regulated kinases/synapsin I signaling cascade [152]. Zhang et al. [134] studied the possible effect of Berberine on middle cerebral artery

Table 2
Berberine: neurological effects.

Sr. no	Pharmacological effects of Berberine	Target/model	Dosage	References
1.	Binds to acetylcholinesterase, butyrylcholinesterase.	Docking studies	NA	[162]
2.	Berberine dilates microvessels and increase the cerebral blood flow of anesthetized mice's meninges	Mice neurons (*In vitro*)		[163]
3.	TetrahydroBerberine inhibits acetylcholine-induced K^+ current in hippocampal CA1 pyramidal neurons.	Rat hippocampal cells		[138]
4.	Alters cell morphology and expression of PLC B1, B3 G-alpha-q/11 in NT-2 Cells	Cell culture system		[164]
5.	TetrahydroBerberine inhibits intracellular message mediated outward currents.	Rat hippocampal cells		[137]
6.	Attenuates glucose neurotoxicity and promotes Nrf2-related neurite outgrowth	Cell culture system	0.1–10 nM	[131]
7.	Promotes neurite formation.	PC-12 Cells/mice	100 ng/ml	[165]
8.	Promotes cell survival in developing brain cells.	MK-801/mice	1.5–3.0 μg/ml	[148]
9.	ProtoBerberine alkaloids help in binding at GABA A site of hippocampus	*In vitro*		[166]
10.	Neuroprotection against ischemic brain damage	Mice	20 mg/kg	[130]
11.	Axonal regeneration	Mice	20 mg/kg	[143]
12.	Improves memory in Alzheimer's disease model	Mice	50–100 mg/kg	[144]
13.	Ameliorate scopolamine-induced neuronal impairment and memory dysfunction	Mice	100–200 mg/kg (male)	[145]
14.	Attenuate Brain injury in aluminum induced rat model	Mice	110 mg/kg	[141]
15.	Protection of cholinergic system in rat model of streptozotocin-induced diabetes	Mice	25–100 mg/kg	[146]
16.	Activates neurons by blocking K^+ current	Mice		[136]
17.	Protects neurons against ischemia	Gerbil	300 mg	[87,132, 149,153]
18.	Antidepressant	Mice	20 mg/kg	[167]
19.	Anxiolytic	Mice	100, 500 mg/kg	[168]
20.	Inhibits nicotine-induced behavioral sensitization	Mice	100 mg/kg	[151]
21.	Sensitizes neurons to glutamate and rotenone injury	Mice		[125]
22.	Inhibits release of glutamate in nerve terminals from cerebral cortex	Mice		[152]
23.	Neuroprotective in autoimmune encephalomyelitis	Mice		[154]
24.	Antipsychotic	Mice		[169]
25.	Acts as deterrent compound against feeding sugar meal of African *Anopheles gambiae*	Mosquito		[170]
26.	Undergoes anti-apoptosis during hypoxia by hypoxia inducible factor-1	Mice		[134]
27.	Anti-apoptotic effect	Mice	100 mg/kg/day	[147]
28.	Activates Nrf2 nuclear translocation and protects against oxidative damage *via* a phosphatidylinositol 3-kinase/Akt-dependent mechanism in NSC34 motor neuron-like cells.	Mice		[135]
29.	Combined with evodiamine, increases 5-HTT RNA and protein expression in various alleles	Mice		[171]
30.	TetrahydroBerberine blocks ATP-sensitive K^+ channels in dopamine neurons which were acutely-dissociated	Mice		[139]
31.	Potential to inhibit Courtship	Drosophila melanogaster	0.5 μg	[172]
32.	Suppresses the OGD-induced increase of p-Bcl-2 level in OHSCs when tissue was exposed to the alkaloid prior to OGD or simultaneously with OGD	Mice	5, 25 mM	[133]
33.	Anti-inflammatory activity	Mice		[150]
34.	Berberine transport uses organiccation transporter in neurons	Mice		[173]
35.	Acts differently in plasma and in hippocampus	Mice		[120]
36.	Uptake (Coptidisrhizoma) by neurons is concentration and time dependent but transportation rate is variable	Mice		[174]
37.	Tetrohydroberbin protects from apoptosis induced by beta-AP by reducing hippocampal neuronal intracellular free Ca^{2+}.	Mice		[175]
38.	High affinity for binding to D_1 and low for D_2 receptors and acts antagonistically.	Mice		[176]
39.	TetrahydroprotoBerberine-143 has highest antagonist action on D_2 receptors	Rat		[177]
40.	Ameliorates β-amyloid pathology, gliosis, and cognitive impairment in an Alzheimer's disease.	Transgenic Mice		[155]
41.	Protective potential against the reserpine-induced nociceptive and depressive behavior.	Mice	1 mg/kg SC	[178]

occlusion-induced ischemic rat. They found that the down-regulation of HIF-1α and p53 are core mechanisms underlying the antiapoptotic effect of Berberine [134].

The treatment with Berberine is also reported to ameliorate hippocampal neuronal damages induced by transient global ischemic damages through the inhibition of matrix metalloproteinase-9 and gelatinase activities [153]. The treatment with Berberine downregulated Laminin and NeuN expression in hippocampal CA1 and CA2 area [153].

Jiang et al. [154] studied the therapeutic effect of Berberine administration in experimental models of multiple sclerosis. They found that the administration of Berberine to a female C57 BL/6 mouse suffering from autoimmune encephalomyelitis protects the brain parenchyma against neuronal damages by inhibiting gelatinase activity, matrix metalloproteinase-9 and laminin degradation [154]. The promising effect of Berberine opens new therapeutic windows for multiple sclerosis.

Durairajan et al. [155] used a transgenic mouse model of AD, TgCRND8 mice, to evaluate the possible effect of Berberine treatment against cognitive impairment and neuropathology. They found that a 4 month daily treatment with Berberine significantly enhances memory function, spatial memory retention, plaque load. They also found that Berberine treatment decreases detergent-soluble and -insoluble β-amyloid in mice brain and it downregulates Glycogen synthase kinase-3. They also reported that Berberine treatment to N2a-SwedAPP cells, down-regulates C-terminal fragments and the hyperphosphorylation of amyloid precursor protein and tau through Akt/glycogen synthase kinase 3 pathways. They concluded that the promising effect of Berberine on Alzheimer's disease may be due to its ability to regulate amyloid precursor protein processing [155].

On the basis of the literature (aforementioned), is clear that Berberine has a strong effect on neurite outgrowth, axonal remyelination and regeneration of neurons in various areas. In addition to the neuroprotective effect, Berberine has been reported to have wide range of additional pharmacological activities which are useful to treat nervous system disorders as shown in Table 2. Therefore, Berberine can be a potential candidate in the treatment of neurodegenerative diseases. Further studies on side effects and on the optimum dosages required for therapeutic purposes currently represent the main focus.

Conclusion and recommendations

With this review we want to provide the reader with a perspective on the protective role of Berberine in neurodegenerative diseases. Literature clearly shows that the neuroprotective role of Berberine is primarily due to its antioxidant and anti-inflammatory activity, though additional mechanism(s) cannot be ruled out. Neurodegenerative disorders are related to old age, even though metabolic disorders including diabetes, dyslipidemia and other cardiovascular disorders are common also in younger patients. Due to the promising effect of Berberine in the above mentioned disorders and to several side effects of polypharmacy, much attention has been paid to its therapeutic role. Despite its high therapeutic potential against neurodegeneration, so far there no clinical trial has been carried out on the neuroprotective effect of Berberine. Therefore, drawing clear, meaningful conclusions about the clinical efficacy of Berberine in patients who suffered from neurodegenerative diseases is still premature. However, the use of Berberine in humans has been fully studied for the treatment of different disorders and it is considered safe even at high doses; for this reason, future studies should be performed on the neuroprotective effects of Berberine in patients affected by neurodegenerative diseases. We also recommend further studies on the following points:

- Clinical trials that should be focused on the neuroprotective role of Berberine.
- Pharmacokinetics including studies on the bioavailability and pharmacodynamics of Berberine and its derivatives in neurological disorders.
- Studying the bioavailability of Berberine using nanoparticles, phospholipid complex and their analogs.
- Finding the optimum effective dose for the neuroprotective role of Berberine and its derivatives.

Conflict of interest

The author(s) confirm that this article content has no conflicts of interest.

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