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REVIEW ARTICLE

Combating Neurodegenerative Diseases with the Plant Alkaloid Berberine: Molecular Mechanisms and Therapeutic Potential

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Abstract: Neurodegenerative diseases are among the most serious health problems affecting millions of people worldwide. Such diseases are characterized by a progressive degeneration and / or death of neurons in the central nervous system. Currently, there are no therapeutic approaches to cure or even halt the progression of neurodegenerative diseases. During the last two decades, much attention has been paid to the neuroprotective and anti-neurodegenerative activities of compounds isolated from natural products with high efficacy and low toxicity. Accumulating evidence indicates that berberine, an isoquinoline alkaloid isolated from traditional Chinese medicinal herbs, may act as a promising anti-neurodegenerative agent by inhibiting the activity of the most important pathogenic enzymes, ameliorating intracellular oxidative stress, attenuating neuroinflammation, triggering autophagy and protecting neurons against apoptotic cell death. This review attempts to summarize the current state of knowledge regarding the therapeutic potential of berberine against neurodegenerative diseases, with a focus on the molecular mechanisms that underlie its effects on Alzheimer's, Parkinson's and Huntington's diseases.

Keywords: Neurodegenerative diseases, berberine, neuroprotection, oxidative stress, neuroinflammation, autophagy.

1. INTRODUCTION

Berberine is a natural isoquinoline alkaloid that is widely present in the roots, rhizomes, stems, or bark of various medicinal herbs such as Berberis, Coptis chinensis, Phellodendron amurense and Hydrastis Canadensis (Fig. **1**) [1-5]. For more than 2,000 years, these plants have been used in Chinese traditional medicine (TCM) to treat a variety of diseases [6]. However, it was not until recently that berberine was isolated and identified as the major pharmacologically active compound of these herbs [6]. Berberine has been shown to possess a wide range of pharmacological activities including anti-microbial, anti-inflammatory, anti-oxidant, hypoglycemic, hypolipidemic, and hepatoprotective properties [7, 8]. It has been tested clinically in the treatment of diarrhea, ulcerative colitis, gastritis, metabolic syndrome, type 2 diabetes mellitus, polycystic ovary syndrome, hypercholesterolemia, hyperlipemia, non-alcoholic fatty liver disease, heart diseases, and so on [6-8].

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Although pharmacokinetic studies of berberine in animals indicate that berberine is not easily absorbed by the gut wall and is present at a very low level in blood, the concentration of berberine as well as its active metabolites was found to be higher in tissues than that in the blood after oral administration [9-11]. In a recent study, Tan and colleagues have systematically analyzed tissue distribution of berberine and its bioactive metabolites in rats after oral administration (200 mg/kg) and have shown that berberine was quickly distributed in the liver, kidneys, muscle, lungs, brain, heart, pancreas, and fat in descending order of its amount [11]. The concentration of berberine in liver was more than ten times of that in plasma, with a peak (68.19 ng/g) observed at 8h after oral administration [11]. They further showed that berberrubine, thalifendine and jatrorrhizine were the major bioactive metabolites of berberine and the level of AUC(0-t) (area under the concentration-time curve) for the metabolites in the liver was 30-fold higher than that in plasma [11]. The tissue distribution profile of berberine and its metabolites provides at least a partial explanation for the discrepancy between poor bioavailability of berberine and its pharmacological effects.

More recently, berberine has been extensively investigated for its therapeutic efficacy against neurodegenerative diseases [12-17]. Accumulating evidence indicates that ber-

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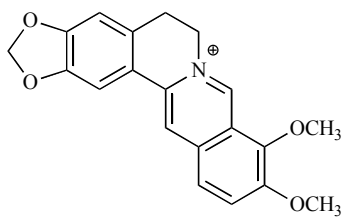

Fig. (1). Molecular structure of berberine.

berine can penetrate the blood-brain barrier under normal physiological conditions and exert neuroprotective effects in both cellular and animal models of Alzheimer's, Parkinson's and Huntington's diseases [12-21]. Recent research into berberine's neuropharmacology suggests that the neuroprotective properties of berberine are probably due to its ability to inhibit the activity of the most important pathogenic enzymes, to reduce intracellular oxidative stress, and to attenuate the inflammatory response [22-30]. In addition, most recent studies have showed that berberine can also combat neurodegenerative diseases by accelerating the clearance of toxic misfolded and aggregated proteins in neuronal cells through induction of autophagy [31, 32]. This review attempts to summarize the current state of knowledge regarding the therapeutic potential of berberine against neurodegenerative diseases, with a focus on the molecular mechanisms that underlie these effects in Alzheimer's, Parkinson's and Huntington's diseases.

2. BERBERINE AND ALZHEIMER'S DISEASE

Alzheimer's disease (AD) is an irreversible, progressive, neurodegenerative disease that gradually erodes memory, cognitive skills, and eventually the ability to carry out simple, everyday tasks [33, 34]. It is the most common cause of dementia, accounting for 60-80% of all cases of dementia in the elderly [35]. According to the Alzheimer's Disease International (ADI), nearly 44 million people are currently afflicted with Alzheimer's or a related dementia worldwide, and it is predicted that the number of individuals affected by AD will quadruple over the next 50 years due to the coming acceleration of global population ageing [35].

The past three decades have witnessed remarkable advances in our understanding of the pathophysiology of AD; however, the etiology of the disease is still mostly unknown [36, 37]. To date, three major hypotheses (cholinergic hypothesis, amyloid hypothesis and tau hypothesis) have been proposed regarding the pathogenesis of AD, which postulate that deficits in the brain neurotransmitter acetylcholine, extracellular deposition of beta-amyloid (Aβ), and intracellular aggregation of tau protein played significant roles in the pathophysiology of the disease [38-41]. Apart from these major hypotheses, there is growing evidence suggests that neuroinflammation, oxidative stress and high levels of serum cholesterol are also implicated in the etiology of AD [42-46].

Since multiple pathogenetic factors are involved in the disease, the current therapeutic strategies for AD that target only a single neurotoxic factor or pathway have been proved to be inadequate [47]. It is, therefore, extremely valuable to consider developing drugs that target multiple factors implicated in AD pathogenesis [48-52]. Recently, several lines of evidence have suggested that berberine may act as a promising multipotent agent to combat AD due to the multiple activities that it possesses, including acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) inhibitory activity, β-site amyloid precursor protein cleaving enzyme 1 (BACE1) inhibitory activity, Glycogen synthase kinase 3 (GSK-3) inhibitory activity, anti-inflammatory activity, antioxidant activity, and cholesterol-lowering activity [1, 12-14, 22-29].

2.1. Berberine Alleviates Cholinergic Deficit and Improves Neurotransmission

Acetylcholine, the first neurotransmitter ever to be identified, is synthesized from choline and acetyl-coenzymeA in presynaptic neurons by the enzyme cholineacetyltransferase [53, 54]. Once released, acetylcholine is rapidly broken down by AChE and BChE [55, 56]. For more than three decades, the pathogenesis of AD has been linked to acetylcholine deficiency in the brain [38]. AChE and BChE inhibition have recently been documented as critical targets for the effective management of AD by alleviating cholinergic deficit and improving neurotransmission [57-61]. As a result, three cholinesterase inhibitors (Donepezil, Galantamine and Rivastigmine) were approved by the Food and Drug Administration (FDA), which constituted the first group of drugs for the symptomatic treatment of AD [62-64]. Recently, a number of studies have shown that berberine exhibited significant AChE inhibitory effects with IC50 values ranging between 0.37 and 0.58 mM, which were comparable to that of Galanthamine (0.59-0.62 mM) [14, 22, 23, 65, 66]. Moreover, Ji *et al*. applied a computational pharmaceutical analysis to reveal that berberine has a much higher Dock score and possesses higher AChE inhibitory activity than the FDA-approved Alzheimer's drug Donepezil [23]. Although some studies indicated that berberine had only weak inhibitory activity against BChE, in a recent study, Jung *et al.* oberserved a potent inhibitory effect of berberine on BChE with an IC50 value of 3.44 mM [67]. In addition to functioning as a powerful dual inhibitor of AChE and BChE, berberine has also been identified as a promising candidate for Aβ and tau-based therapeutics to prevent or delay the onset of Aβ and tau pathology in AD [22, 26-28, 32].

2.2. Berberine Inhibits Aβ Generation and Senile Plaques Formation

Aβ peptide is a proteolytic product derived from the sequential cleavage of Aβ precursor protein (APP) by β-secretase (also known as BACE1) and γ-secretase, whereas α-secretase precludes its generation through alternative cleavage of APP within the Aβ sequence [68-70]. The progressive accumulation and aggregation of Aβ in the extracellular space leads to the formation of senile plaques, one of the hallmark lesions of AD [71-73]. Therefore, inhibition of Aβ generation and/or aggregation should be a rational therapeutic strategy for AD [74, 75]. Accumulating evidence suggests that berberine can reduce Aβ peptide production by modulating APP processing, and can prevent amyloid fibril formation by inhibiting Aβ aggregation [26, 28, 32, 76, 77]. Asai and colleagues reported that berberine treatment effectively reduced levels of Aβ in

human neuroglioma H4 cells that stably express Swedish-type of APP, with an IC50 of around 5 μM [76]. They further demonstrated that this reduction was modulated by berberine through both down-regulation of β-secretase (BACE1) activity and up-regulation of α-secretase activity, leading to a shift in the processing of APP from the amyloidogenic to the non-amyloidogenic pathway [76]. Using Swedish APP-expressing HEK293 cells, Zhu *et al.* showed that berberine decreases the production of Aβ by inhibiting the expression of BACE1 *via* activation of the ERK1/2 pathway [78]. Inhibition of ERK1/2 with the MEK1/2 antagonist, U0126, could abolish the effects of berberine on both Aβ and BACE1 [78]. A recent study by Zhang *et al.* found that the AMP-activated protein kinase (AMPK) pathway was also involved in berberine-modulated metabolism of Aβ. Through the activation of AMPK, berberine down-regulatd the expression of BACE1 and reduced Aβ generation in neuroblastoma cells and primary cultured neurons [79]. Recently, the efficacy of berberine on the modulation of APP processing and Aβ-induced neurotoxicity was further validated in several *in vivo* models [26, 28, 80]. Using an Almaltol-induced AD rabbit model, Panahi *et al.* showed that berberine treatment could significant decrease the activity of BACE1, protect the hippocampus from degeneration, and restore chemically-induced AD-like behavioral derangements [28]. Similarly, Haghani *et al.* created a rat model of AD by bilateral injection of Aβ in the prefrontal cortex and investigated the effects of berberine on the Aβ-induced cognitive impairment and neurotoxicity [80]. Their results suggested that the administration of berberine could ameliorate neurotoxicity induced by Aβ through prevention of the impairing impacts of Aβ on the learning, memory, as well as electrophysiological properties of the hippocampal pyramidal neurons [80]. Moreover, in a recent study Durairajan *et al.* demonstated that chronic administration of berberine not only reduced Aβ deposits, but also ameliorated tau hyperphosphorylation, gliosis, and cognitive impairments in a well characterized transgenic mouse model of AD (TgCRND8 mice) [26]. They also found that these effects were achieved mainly through regulation of APP processing *via* the PI3K/Akt/GSK3 signaling pathway [26]. Berberine treatment led to the activation of PI3K/Akt, which subsequently inactivated glycogen synthase kinase 3(GSK3) *via* modulation of its phosphorylation status, resulting in reduced levels of p-APP and Aβ [26].

2.3. Berberine Inhibits Tau Hyperphosphorylation and Neurofibrillary Tangles Formation

It is noteworthy that, as an inhibitory target of berberine, GSK3 not only plays an important role in modulating APP processing and influencing the production of Aβ, but also contributes to hyperphosphorylation of tau, which leads to the transformation of normal tau protein into paired helical filament and neurofibrillary tangles, another hallmark lesion of AD [81-83]. The phosphorylation status of tau is the result of a balanced action between protein kinases and protein phosphatases, therefore, it is no surprise to find that over-activation of glycogen synthase kinase 3 beta (GSK-3β) and/or inhibition of protein phosphatase 2A (PP2A) have been frequently reported to induce tau hyperphosphorylation [84-88]. In a recent study, Yu *et al.* treated tau-expressing HEK293 cells with calyculin A, a potent inhibitor of PP2A and PP1, and created a cellular model of tauopathy to investigate the roles of berberine in tau hyperphosphorylation [89]. They showed that calyculin A treatment not only inhibited PP2A, but also activated GSK3β by phosphorylating it on Tyr216 and dephosphorylating it on Ser9, which subsequently led to tau hyperphosphorylation at multiple sites [89]. Berberine significantly attenuated calyculin A-induced tau hyperphosphorylation and cytotoxicity through restoration of PP2A activity and reversal of GSK3β activation [89]. Consistent with these findings, Liu *et al.* reported that berberine rescued the decrease in PP2A activity by reversing the phosphorylation of PP2A on Tyr307, which in turn alleviated tau hyperphosphorylation and axonal transport impairment induced by calyculin A [16].

3. BERBERINE AND PARKINSON'S DISEASE

Parkinson's disease (PD) is the second most prevalent neurodegenerative disorder, which affects approximately 7 million people worldwide [90-92]. There are four cardinal motor symptoms of PD that can be grouped under the acronym TRAP: Tremor at rest, Rigidity, Akinesia (or bradykinesia) and Postural instability [93, 94]. In addition, PD can also give rise to several non-motor dysfunctions that include hyposmia, cognitive difficulties, autonomic disturbances and sleep disorders [95, 96]. It is suggested that the primary symptoms of PD result from the selective loss of dopaminergic neurons in the substantia nigra and the formation of Lewy bodies in many of the remaining neurons due to an abnormal accumulation of alpha-synuclein protein [97-105]. Although we have gained a relatively large amount of knowledge on the pathophysiology of PD, the etiology of the disease remains elusive [106-108]. Due to poor understanding of its pathogenesis, there is no treatment to halt or reverse the progression of PD [106-108].

Most of the current therapies are limited to symptomatic relief of the disease by restoring levels of dopamine in the brain and, in this respect, levodopa, dopamine agonists and monoamine oxidase B (MAO-B) inhibitors represent first-line pharmacological options [109-113]. Levodopa is the metabolic precursor of dopamine and it can cross the blood–brain barrier, whereas dopamine itself cannot [114]. Once entered the central nervous system, levodopa can be taken up by dopaminergic neurons and converted into dopamine by 3,4-Dihydroxyphenylalanine (DOPA) decarboxylase [114]. The administration of levodopa temporarily restores striatal dopaminergic neurotransmission and alleviates symptoms of PD [115]. This alleviation can also be accomplished by dopamine agonists, compounds that directly activate postsynaptic striatal dopamine receptors, thus obviating the need for dopamine production [116]. Monoamine oxidases (MAO) are a family of mitochondrial enzymes, which catalyze the oxidative deamination of monoamine neurotransmitters such as dopamine and serotonin [117-120]. MAO consists of two different subtypes, MAO-A and MAO-B, which are coded by two distinct genes and have different substrate and inhibitor specificity [118, 119]. In the striatum, the predominant form of MAO is MAO-B, which constitutes about 80% of the total MAO activity in the human brain [118, 119]. Since MAO-B breaks down dopamine, inhibiting it will prolong

the action of dopamine and improve the symptoms of PD [120-122]. Indeed, MAO-B inhibitors, such as selegiline and rasagaline, have been shown to be effective in treating motor symptoms and delay the need for levodopa in early PD [123-128]. However, due to the undesirable adverse effects of the chemically synthesised drugs, searching for natural product-based MAO-B inhibitors would be of great value for the safe treatment of PD [129].

3.1. Berberine Reduces Degradation of Dopamine and Prevents Neurotoxins Induced Dopaminergic Neuronal Death

Inhibition of MAO-A has been related to antidepressant activity, whereas inhibition of MAO-B has been proven to delay onset, or alleviate symptoms of PD [130]. Recent studies have found that berberine exhibits inhibitory activity on both MAO-A and MAO-B [23, 131-133]. Lee *et al.* evaluated the inhibitory effect of berberine on MAO-B and oberserved an IC50 value of 98.2 μM [131]. Similar results were obtained by Castillo and colleagues using the conventional Benzylamine (substrate) method and an alternative LED fluorescence (without substrate) method, reporting IC50 values of 98.4 μM and 90 μM, respectively [132]. Moreover, to elucidate the molecular basis of berberine's inhibitory effects against MAO-B, Ji and coworkers investigated the binding mode of berberine with MAO-B by means of docking simulations [23]. The theoretical binding constant of berberine to MAO-B was estimated to be 66 μM, which was very close to the experimental value [23]. In addition, their results indicate that the binding of berberine to MAO-B is mainly driven by hydrophobic interactions rather than electrostatics interactions [23]. These findings indicate that berberine may reduce degradation of dopamine and alleviate symptoms of PD, at least partly, through its inhibitory effect on MAO-B.

Several *in vitro* and *in vivo* studies enable an overview of possibilities and limitations of berberine as a therapeutic agent against PD [15, 134]. Using an *in vitro* model of PD, Bae *et al.* have demonstrated that berberine protects dopaminergic neurons from cell death induced by the parkinsonism-inducing neurotoxin 6-hydroxydopamine (6-OHDA) [134]. In addition, Kim and colleagues investigated the *in vivo* neuroprotective effects of berberine, with the use of the 1-methyl-4-phenyl-1,2,3,6-trerahydropyridine (MPTP) mouse model of PD that recapitulates several features of the disease [15]. Their studies have suggested that berberine can improve motor balance and coordination by preventing MPTP-induced dopaminergic neuronal death in the substantia nigra and fiber loss in the striatum [15]. They have also demonstrated that berberine can alleviate MPTP-induced short-term memory impairment by inhibiting apoptosis in the hippocampus [15]. Collectively, these studies have shed some light on the possibility of utilizing berberine as a therapeutic agent against PD [15, 134]. It is worth mentioning that, although berberine is generally considered safe for human use, studies by Shin *et al*. from South Korea have raised concerns regarding the adverse effect of chronic L-DOPA-berberine combination therapy in a rat model of PD [135]. In a previous study, they also claimed that berberine aggravated 6-OHDA-induced cytotoxicity in PC12 cells, and led to the degeneration of dopaminergic neuronal cells in the substantia nigra of 6-OHDA-lesioned rats [136]. Although their findings are inconsistent with other studies, which have suggested that berberine protects 6-OHDA or MPTP-induced dopaminergic neuronal loss and suppresses hippocampal apoptosis [15, 134], further studies are required to evaluate the potential adverse effects and limitations of single or combined use of berberine for the treatment of PD.

4. BERBERINE AND HUNTINGTON'S DISEASE

Huntington's disease (HD) is a hereditary neurodegenerative disorder, which is characterized by involuntary motor movement, cognitive impairments and psychiatric disturbances [137, 138]. It is estimated that the worldwide prevalence of HD is 5-10 cases per 100,000 persons, but varies greatly across ethnic groups and geographical locations, with the highest incidence in Western Europe and the lowest in Asia [139]. The cause of the disease has been unknown until fairly recently [140-142]. It is now clear that HD is caused mainly by an autosomal dominant mutation in either of an individual's two copies of a gene called Huntingtin (HTT), which is located on the short (p) arm of chromosome 4 at position 16.3 [143-146]. *HTT* is variable in its structure, as it has many polymorphisms that harbor different number of CAG trinucleotide repeats in exon 1 [147]. Since the CAG trinucleotide is the codon for the amino acid glutamine, a string of CAG results in the production of a polyglutamine (polyQ) tract [147]. The length of the glutamine repeats in normal persons varies from 6 to 35 [148]. Expansion of the polyQ tract to 36 or more glutamine repeats causes HTT protein misfolding, aggregation and neuronal death, resulting in Huntington's disease [149]. In addition, the age of HD onset was found to be inversely correlated with the length of the polyQ tract [150, 151]. Once above the pathogenic threshold, there is a strong negative correlation between the polyQ tract length and the age of HD onset [150, 151].

It is noteworthy that recent studies have suggested a direct correlation between HD progression and defects in the autophagy-lysosomal pathway [152-154]. Macroautophagy (generally referred to as autophagy) is an essential homeostatic process responsible for the degradation of larger structures such as organelles and protein aggregates that the ubiquitin-proteasome system (UPS) is unable to handle [155-156]. During this process, targeted cytoplasmic constituents are sequestered in double-membrane structures called autophagosomes, which then fuse with endosomes and lysosomes, allowing their contents to be degraded and recycled [155-156]. It has been demonstrated that autophagy is a major clearance pathway for the removal of intracytosolic aggregate-prone proteins associated with AD (mutant tau) and PD (mutant a-synuclein) [157-165]. Moreover, recent studies suggest that the autophagy-lysosomal pathway also plays a vital role in the clearance of aggregate-prone mutant form of huntingtin (polyQ-HTT) [152-154]. Multiple independent lines of evidence show the impairment of autophagy during the progression of HD [152-154]. Induction of autophagy enhances the clearance of polyQ-HTT aggregates and alleviates mutant huntingtin-mediated toxicity in Drosophila and mouse models of HD [166-168]. These findings provide a strong rationale for the development of autophagy modulators as a novel strategy to treat or retard progression of HD

and related protein misfolding disorders [169]. Interestingly, berberine has turned out to be a promising autophagy activator. Using a transgenic HD mouse model, Jiang and colleagues showed that berberine could significantly trigger autophagy to remove polyQ-HTT aggregates and, as a result, remarkably ameliorated the neurological phenotypes in the HD mice [31].

5. GENERAL NEUROPROTECTIVE ROLE OF BERBERINE

5.1. Berberine Triggers Autophagy and Enhances the Clearance of Toxic Aggregated Proteins

Recently, berberine has been found to be a potent trigger of autophagy in a wide range of cell types including liver, kidney, breast, myocardium, macrophages, lung, as well as neuron cells [31, 32, 170-189]. Berberine is effective in promoting autophagy, which can attenuate left ventricular remodeling, cardiac dysfunction and cardiomyocyte apoptosis in a rat model of cardiac hypertrophy [175, 176]. By upregulating the levels of autophagy, berberine can also inhibit oxidized low-density lipoprotein (ox-LDL)-induced inflammation in macrophages and provide a therapeutic potential in the treatment atherosclerosis [177-180]. In addition, berberine was reported to stimulate autophagy by inhibiting PI3K/Akt-mTOR signaling cascade, and significantly reduced the degree of pulmonary fibrosis in animal models [181]. Moreover, a growing body of evidence has suggested that berberine also possesses anti-tumor properties and can enhance the effect of certain chemotherapeutic agents and radiotherapy on cancer cells, not only *via* apoptosis but also through the induction of autophagy [182-189].

In a most recent study, Jiang and colleagues examined the effects of berberine on the accumulation of toxic polyQ-HTT in cellular and an animal model of HD [31]. Their results showed that berberine could significantly upregulate autophagy to remove polyQ-HTT both in HEK293 cells transfected with a mutant *HTT* containing 120 CAG repeats in exon1, and in a transgenic HD mouse model expressing mutant HTT containing 82 glutamine repeats in the polyQ tract [31]. The clearance of polyQ-HTT aggregates by autophagy significantly ameliorates the neurological phenotypes in the HD mice, with greatly improved rotarod performance, muscle strength, motor coordination and life span [31].

What is more, using APP/tau/PS1 triple-transgenic mouse model of Alzheimer's disease, Huang *et al*. have showed that berberine also triggers autophagy and facilitates Aβ clearance in the hippocampus of AD mice. They have further showed that berberine enhances autophagy in the brains of triple-transgenic AD mice possibly through the induction of the class III PI3K/Beclin-1 pathway [32]. Interestingly, although a great many studies have indicated that autophagy can be triggered by activating of the AMPK/mTOR pathway, Zhang *et al*. have recently demonstrated that berberine reduces the expression of BACE1 and inhibits the generation of Aβ just *via* activating AMPK, with no effect on mTOR signaling [79].

These findings should promote further investigations aimed at elucidating the therapeutic role of berberine in other neurodegenerative diseases that are also caused by misfolded proteins [32, 174, 178].

5.2. Berberine Inhibits Neuroinflammation

Neuroinflammation is inflammation of the nervous tissue. It may be initiated by a variety of factors, including traumatic brain injury, microbial infections, toxic metabolites, autoimmunity and aging [190-192]. Despite different triggering events, a common feature of neuroinflammation is chronic activation of microglia and astrocytes [193, 194]. In the diseased central nervous system (CNS), microglia and astrocytes are dramatically activated and secrete various pro-inflammatory mediators and neurotoxic cytokines that will cause further damage in neuronal cells, thus creating a vicious self-propagating cycle of neuronal damage and neuroinflammation and contributing to the chronic progression of neurodegenerative diseases [195-197]. It has been hypothesized that inhibiting neuroinflammation could diminish neuronal loss, and this hypothesis is supported by observations that long-term use of non-steroidal anti-inflammatory drugs (NSAIDs) is associated with a significantly lower incidence of neurodegenerative diseases [198-200].

Recently, it was demonstrated that berberine could suppress neuroinflammation, and could be considered as a drug candidate for inflammatory-related CNS disorders [201-205]. Nam *et al*. have found that berberine was effective at inhibiting inflammatory activation of rat brain microglia by suppression of pro-inflammatory cytokines, nitric oxide (NO), and nuclear factor-kappaB (NF-κB) activity [201]. In addition, berberine was also shown to exert significant inhibitory effects on the LPS- or interferon-g-induced production of inflammatory mediators and cytokines, such as inducible nitric oxide synthase (iNOS), cyclooxygenase 2 (COX-2), Tumor necrosis factor-a (TNF-a), Interleukin(IL)-1β, and IL-6 in BV-2 microglia cells, through activation of the AMPK signalling pathway [202, 203]. In consistent with these findings, Jia *et al*. have found that berberine treatment suppressed Aβ-induced inflammatory responses in murine primary microglial cells and BV2 microglia cell line by inhibiting the mitogen-activated protein kinase (MAPK) and the NF-κB signalling pathways [204]. In a recent study, Chen and coworkers has shown that berberine could also attenuate traumatic brain injury (TBI)-induced neuronal damage by inhibiting leukocyte infiltration, microglial activation, and the production of inflammatory mediators [205].

5.3. Berberine Ameliorates Oxidative Stress

Accumulating data shows that oxidative stress plays a crucial role in the onset and progression of neurodegeneration [206-208]. Under the circumstance of oxidative stress, excessive amounts of reactive oxygen species (ROS) and/or reactive nitrogen species (RNS) cause lipid peroxidation, protein oxidation, protein nitration, and glycoloxidation, resulting in plasma membrane damage, cytoskeletal disruption as well as nucleic acids mutations in the nervous tissue [209, 210]. In recent years, increasing attention has been paid to the use of antioxidant compounds to combat neurodegenerative diseases [211-214].

It was reported that berberine possesses potent and diverse antioxidant activities [215-226]. Berberine can effectively reduce intracellular superoxide levels in Lipopolysaccharide (LPS)-stimulated human monocyte-derived macrophages by inhibiting the expression of gp91phox, the catalytic subunit of NADPH oxidase [227]. Berberine has also been shown to reduce NO production in LPS-treated murine macrophages by downregulating the expression of iNOS [228]. In addition, it was found that berberine can also restore the activities of several antioxidant enzymes both *in vitro* and *in vivo*, including superoxide dismutase (SOD), catalase, glutathione S-transferase (GST), and glutathione peroxidase (GSH-Px) [229, 230].

Using NSC34, a motor neuron-like cell line, Hsu *et al*. investigated the *in vitro* neuroprotective effects of berberine. They found that berberine protected NSC34 cells against hydrogen peroxide induced cytotoxicity not only by attenuating ROS production and restoreing GSH and SOD activity, but also by activating anti-oxidant proteins nuclear erythroid 2-related factor 2 (Nrf2) and heme oxygenase-1 (HO-1) [231]. They further explored the protective mechanism of berberine on high glucose-induced oxidative stress and neurite damage of SH-SY5Y cells. Berberine was found to effectively ameliorate high glucose-induced ROS production, nuclear condensation and neuronal cell death, at least in parts, by activating the PI3K/Akt/Nrf2/HO-1-dependent cytoprotective and antioxidant pathways [232]. All the above mentioned studies have established berberine as a potent anti-oxidant molecule, therefore, may have therapeutic effect on neurodegenerative diseases.

5.4. Berberine Protects Neuronal Cells Against Apoptosis

Although a large number of studies have reported that berberine can induce apoptosis in various cancer cells [233, 234], accumulating evidence indicates that berberine plays an important role in inhibiting oxidative stress, high glucose stress or ischemia/reperfusion-induced apoptosis in different types of normal cells [235-243], particularly neuronal cells [244-256].

Using the MPTP mouse model of PD, Kim *et al*. have demonstrated that berberine upregulates the anti-apoptotic protein Bcl-2 and downregulates the pro-apoptotic protein Bax [246]. As a result, it enhanced motor balance and coordination by preventing dopaminergic neuronal death in the substantia nigra of mice with PD, and ameliorated short-term memory impairment by inhibiting neuronal injury and apoptosis in the hippocampus [246]. Berberine has also been shown to attenuate apoptosis of pyramidal neurons in the CA1 area, and ameliorate learning and memory impairment of streptozotocin (STZ)-diabetic rats [247].

Furthermore, berberine exhibits neuroprotective effects against ischemic brain injury by inhibiting neuronal apoptosis in both *in vitro* and *in vivo* models [248-255]. It has been reported that berberine improved neurological outcome and attenuated ischemia/reperfusion (I/R)-induced neuron death by suppressing intracellular ROS generation, or by modulating of PI3K/Akt/GSK3β and JNK signaling pathways, decreasing hypoxia-inducible factor 1α (HIF-1α), caspase 9, caspase 3 activity and increasing Bcl-2/Bax ratio, and as a result, inhibited caspase-dependent and -independent apoptosis pathways [248-255]. In addition, a recent study by Zhang *et al*. has suggested that berberine could also act as a preconditioning stimulus to ameliorate hypoxia/ischemia-induced cerebral damage *via* triggering prosurvival autophagy and suppressing anoxia-induced apoptosis [256]. These findings, therefore, provide a novel perspective for berberine to combat neurodegenerative diseases.

CONCLUSION AND FUTURE PERSPECTIVES

Neurodegenerative diseases are among the most serious health problems affecting millions of people worldwide [257]. Such diseases are characterized by a progressive degeneration and/or death of neurons in the central nervous system [258]. Currently, there are no therapeutic approaches to cure or even halt the progression of neurodegenerative diseases [259]. During the last two decades, much attention has been paid to the neuroprotective and anti-neurodegenerative activities of compounds isolated from natural products with high efficacy and low toxicity [260-263]. Accumulating evidence indicates that berberine, an isoquinoline alkaloid isolated from traditional Chinese medicinal herbs may act as a promising anti-neurodegenerative agent.

Here, we reviewed the current state of knowledge regarding the therapeutic potential of berberine against neurodegenerative diseases, with a focus on the molecular mechanisms that underlie its effects on Alzheimer's, Parkinson's and Huntington's diseases. In summary, previous studies have clearly showed that berberine exerts neuroprotective effects primarily by inhibiting the activity of several important pathogenic enzymes (such as AChE, BChE, BACE1, GSK-3 and MAO-B), ameliorating intracellular oxidative stress, attenuating neuroinflammation and inhibiting apoptotic cell death. Berberine can also combat neurodegenerative diseases by accelerating the clearance of toxic misfolded and aggregated proteins in neuronal cells through induction of autophagy (Fig. **2**). In addition, berberine has been tested clinically in the treatment of diarrhea, metabolic disorders, cardiovascular diseases, type 2 diabetes mellitus, polycystic ovary syndrome, hypercholesterolemia, hyperlipemia, and non-alcoholic fatty liver disease for many years, and it is generally considered to be effective and safe at doses used in clinical situations, with no cytotoxic, genotoxic or mutagenic activity being detected [264-275]. Furthermore, berberine can be administered orally and it can easily pass through the blood-brain barrier [276].

Although clinical trials of berberine have been performed in several diseases including, diarrhea, metabolic syndrome, diabetes, congestive heart failure, and radiation-induced acute intestinal symptoms and these studies reinforce its safety profile with zero death rate and no or minor gastrointestinal adverse effects, clinical studies of berberine against CNS disorders are still lacking [277-281]. Extensive preclinical data summarized in this review should provide a convincing basis for conducting clinical trials of berberine against neurodegenerative diseases in the near future. On the other hand, the clinical application of berberine is greatly limited due to poor gastrointestinal absorption and bioavailability after oral administration, novel dosage forms of ber-

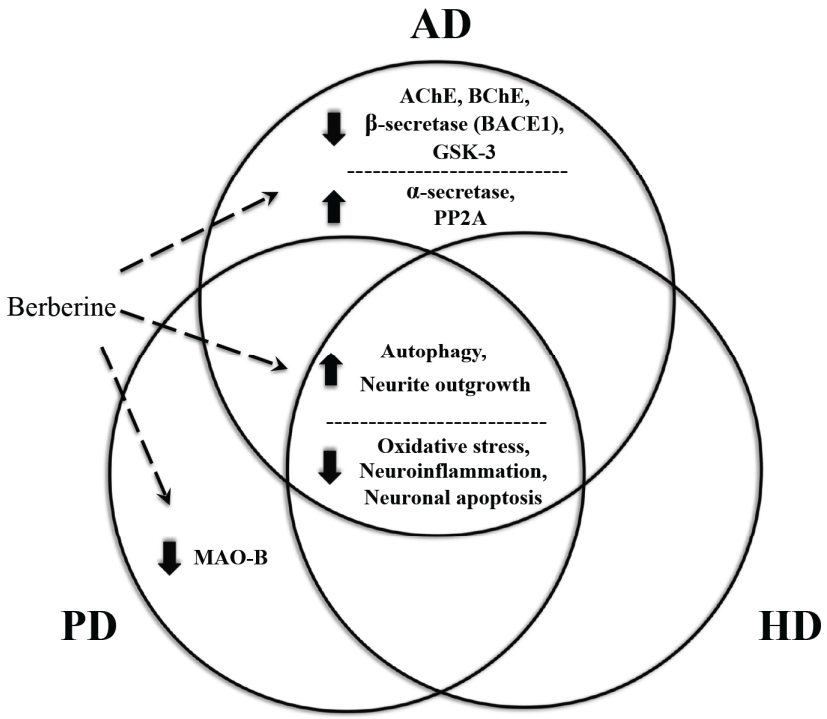

Fig. (2). Common and distinct molecular mechanisms underlying berberine's capability of combating AD, PD and HD. Excessive oxidative stress, neuroinflammation, apoptosis and insufficient autophagy are common pathologic features that are shared by neurodegenerative diseases and can be targeted by berberine in common. In addition, berberine can inhibit the activity of several important but distinct pathogenic enzymes in AD, PD and HD, including AChE, BChE, BACE1, GSK-3 and MAO-B.

berine that can overcome these barriers is needed. Recently, nanotechnology drug delivery approach of berberine has been shown to improve the drug pharmacokinetic performance and the intended target outcome [282-286]. Future studies should also be focused on testing different type of nanoparticles and nanoformulation of berberine to improve the bioavailability, pharmacological activities, efficacy and selectivity of berberine and/or its derivatives in clinical settings.

LIST OF ABBREVIATIONS

6-OHDA	=	6-hydroxydopamine
AChE	=	Acetylcholinesterase
AD	=	Alzheimer's Disease
ADI	=	Alzheimer's Disease International
AMPK	=	AMP-Activated Protein Kinase
APP	=	Amyloid-β Precursor Protein
Aβ	=	Amyloid-β
BACE1	=	β-site Amyloid Precursor Protein Cleaving Enzyme 1
BChE	=	Butyrylcholinesterase
CNS	=	Central Nervous System
COX-2	=	Cyclooxygenase 2
DOPA	=	3,4-Dihydroxyphenylalanine
FDA	=	Food and Drug Administration
GSH-Px	=	Glutathione Peroxidase
GSK-3	=	Glycogen Synthase Kinase 3
GST	=	Glutathione S-Transferase
HD	=	Huntington's Diseases
HIF-1α	=	Hypoxia-Inducible Factor 1α
HO-1	=	Heme Oxygenase-1
HTT	=	Huntingtin
IL	=	Interleukin
iNOS	=	inducible Nitric Oxide Synthase
LPS	=	Lipopolysaccharide
MAO	=	Monoamine Oxidase
MAPK	=	Mitogen-Activated Protein Kinase
MPTP	=	1-Methyl-4-Phenyl-1,2,3,6-Trerahydropyridine
NF-κB	=	Nuclear Factor-kappaB
NO	=	Nitric Oxide
Nrf2	=	Nuclear Erythroid 2-Related Factor 2
NSAIDs	=	Non-Steroidal Anti-Inflammatory Drugs
ox-LDL	=	Oxidized Low-Density Lipoprotein

PD	=	Parkinson's Diseases
polyQ	=	polyglutamine
PP2A	=	protein Phosphatase 2A
RNS	=	Reactive Nitrogen Species
ROS	=	Reactive Oxygen Species
SOD	=	Superoxide Dismutase
STZ	=	Streptozotocin
TCM	=	Chinese Traditional Medicine
TNF-a	=	Tumor Necrosis Factor-a

DECLARATIONS

Ethics Approval and Consent to Participate

This review summarizes published studies using human and animal material. Research studies in this review were approved by the appropriate ethics committees.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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