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Neuroprotective effect of berberine based on the Alzheimer's disease model

Abstract. Berberine, an isoquinoline alkaloid, is a substance used in traditional East Asian folk medicine. It is naturally found in many plant species, especially those of the Berberis genus. It has multifaceted anti-inflammatory and neuroprotective properties. The ageing population is currently affected by the growing prevalence of neurodegenerative diseases, the most common of which is Alzheimer's disease. Berberine provides multidirectional protective and therapeutic effects against pathological neuronal changes. Its application reduces the synthesis of amyloid-β and tau protein plaques. In addition, it exhibits an effect typically associated with drugs currently used to treat this disease – cholinesterase inhibition. It has been shown that the use of berberine reduces inflammation in nervous tissue, inhibits apoptosis mechanisms and promotes neuronal repair processes. However, further preclinical studies are required to assess its efficacy and toxicity.

Keywords: berberine, memory, Alzheimer's disease

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INTRODUCTION

Berberine (molecular formula $C_{20}H_{19}NO_5$, 353.36 g/mol) is a chemical substance that, along with papaverine and noscapine, among others, belongs to the group of isoquinoline alkaloids (Fig. 1). It occurs naturally mainly in the stems and roots of various plants belonging to the *Berberis* genus: *B. asistata*, *B. petiolaris*, *B. vulgaris*, *B. darwinii* – this is its most common natural source [Singh et al. 2019]. In addition, it can be isolated from plants of the *Annonaceae*, *Menispermaceae*, *Papaveraceae*, *Ranunculaceae* and *Rutacea* families. It accumulates mainly in the roots and bark, but is also present in the leaves, rhizomes and stems of the plant. After isolation, it is available as a yellow or orange powder with a crystalline structure, emitting a characteristic low-intensity odour and a bitter taste. The toxicity of berberine is minimal [Tajiri et al. 2021]; in rodents, the LD_{50} is 200 mg/kg with no concomitant hepatotoxicity [Amat-Ur-Rasool et al. 2021a].

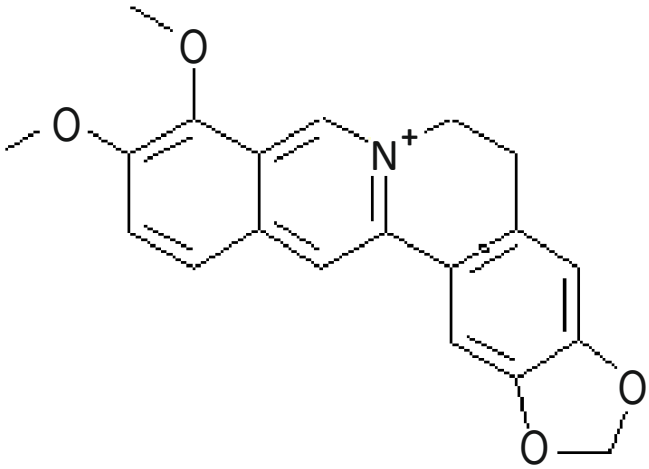

Fig. 1. Chemical structure of berberine (according to the ChemSpider database)

Berberine has been commonly used in traditional Chinese medicine for thousands of years. In China, Berberis is called ‘Huangbai’ and is broadly used as a therapeutic agent for gastrointestinal disorders, respiratory and skin inflammations [Wang et al. 2024]. Ayurvedic and other East Asian folk medicine practices also indicate the possibility of using berberine as a therapeutic agent for eye, ear and oral diseases, skin wounds and infections [Neag et al. 2018]. However, berberine does not cross the blood-brain barrier by passive diffusion due to the presence of a charged nitrogen atom, but its derivatives, e.g. ether, sulfonyl and carbonyl derivatives, possess this ability [Sobolova et al. 2020, Raghuvanshi et al. 2023]. Ether derivatives, which are a more stable form of berberine in the human body, are characterised by low internal clearance values (<8 µl/min/mg protein) and high hepatic elimination coefficient values (>0.7) [Raghuvanshi et al. 2023]. In addi-

tion, blood-brain barrier endothelial cells express the lactoferrin (Lf) receptor, which enables an increase in the concentration of the drug delivered to the CNS by modifying it with Lf [Mittal et al. 2020]. Another way to modify berberine molecules is to create nanoliposomes. Their additional modification with Lf also significantly increases the accumulation of these molecules in the brain [Singh et al. 2021, Wang et al. 2023].

ALZHEIMER'S DISEASE

Neurodegenerative diseases are caused by permanent damage and loss of neurons in the central nervous system. They are characterised by a negative impact on both the clinical condition and quality of life of the patient, mainly through cognitive impairment. The most common neurodegenerative disease is Alzheimer's disease, which is more common in older people and accounts for 60–80% of dementia cases [DeTure and Dickson 2019]. In 2018, it affected almost 9 million people in Europe, and predictions for 2025 estimate over 10 million patients [Alzheimer Europe 2019]. Globally, this problem affects 57 million people, and predictions for 2050 indicate 152 million patients [GBD 2019 Dementia Forecasting Collaborators 2022]. The disease can occur both genetically and sporadically, and its incidence increases with age among both women and men [Alzheimer Europe 2019].

Alzheimer's disease (AD) is a slowly progressive disease that causes irreversible destruction of neurons responsible for storing and processing information. Clinically, it manifests itself as dementia, characterised by significant impairment of cognitive functions in several areas and neurobehavioural symptoms affecting the functioning of the individual [Scheltens et al. 2021]. The disorders mainly affect memory functions – in terms of learning new information, but also „memory, thinking, orientation, comprehension, calculation, learning capacity, language, and judgement" [World Health Organisation 2019].

THE EFFECT OF BERBERINE ON THE PATHOGENESIS OF ALZHEIMER'S DISEASE

Berberine has a multidirectional effect on the Alzheimer's disease model (Fig. 2). Substances isolated from *Fibraurea recisa Pierre* are characterised by their ability to bind to proteins that are key to the pathogenesis of this disease, and correlation analysis has identified many potential targets for therapeutic action [Wang et al. 2022].

Amyloid and tau protein

Berberine inhibits the activity of β-secretase (BACE-1), an enzyme that cleaves the amyloid precursor protein, leading to the formation of amyloid-β (Aβ) [Chu et al. 2018, Lin et al. 2020, Singh et al. 2021, Wu et al. 2021], however, Liang et al. [2021] did not observe such an effect. According to them, the effect of reducing Aβ production is achieved by reducing the synthesis of the BACE-1 protein [Ge et al. 2020, Liang et al. 2021]. The effect of berberine on BACE-1 can be enhanced by modifying and introducing carbonyl or sulfonyl groups, which increases the inhibitory activity of the derivatives

[Raghuvanshi et al. 2023]. This phenomenon occurs as a result of the strengthening of bonds formed during interactions, including hydrogen bonds. The inhibition of BACE-1 results in the inhibition of Aβ production and a reduction in its amount detected in hippocampal neurons in immunohistochemical studies [Liang et al. 2021, Wu et al. 2021]. Berberine also increases the expression of circular RNA molecules – circHDAC9, which leads to a decrease in the concentration of miR-138, which stimulates the production of Aβ [Zhang et al. 2020]. The decrease in Aβ concentration in the cerebral cortex and hippocampus can be enhanced by the synergistic action of berberine and curcumin [Lin et al. 2020]. Furthermore, the use of berberine enables concentration-dependent chelation of Cu^{2+} involved in Aβ aggregation, also by inhibiting the formation of oligomers with the highest toxic potential through interaction with protofibrils [Chu et al. 2018, Rajasekhar et al. 2020]. Ether analogues of berberine have the ability to inhibit Aβ aggregation by 74%, while berberine alone achieves inhibition values of 32% [Sobolova et al. 2020, Singh et al. 2021, Tajiri et al. 2021, Raghuvanshi et al. 2023].

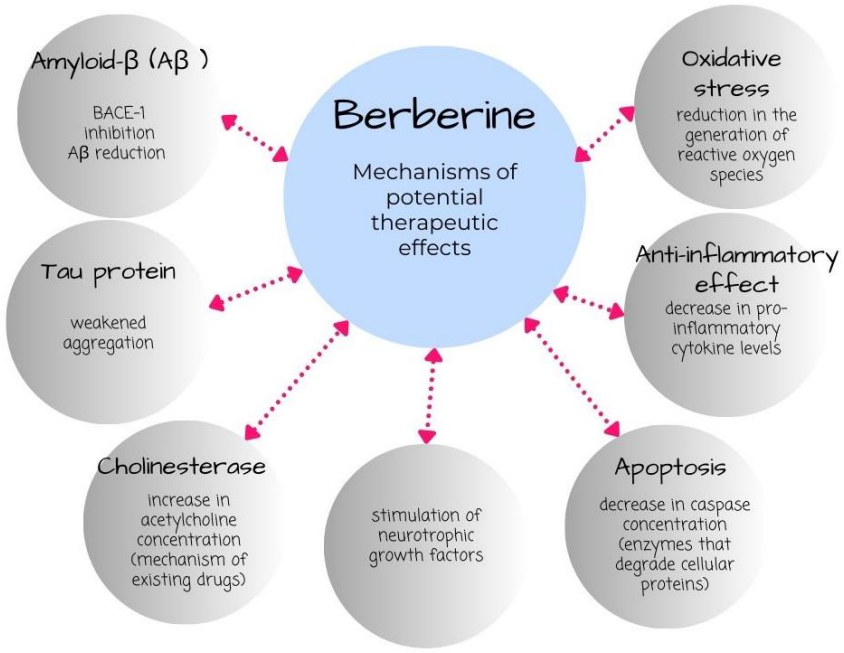

Fig. 2. Berberine – mechanisms of potential therapeutic effects

A reduction in the number of cells with phosphorylated tau protein deposits may occur after administration of berberine in solution form, and especially in the form of modified Lf nanoliposomes [Wang et al. 2023]. Berberine reduces hyperphosphorylation of tau protein at Thr205, which is involved in neurofibrillary degeneration [Yang and Wang 2022], and weakens its aggregation [Sobolova et al. 2020]. It also reduces the activity of glycogen synthase kinase 3β by phosphorylating it [Wu et al. 2021, Yang and Wang 2022] and by stimulating the expression of miR-107, which reduces the level of zinc finger protein (ZNF217) that weakens apoptotic signals [Wang and Jin 2019].

Cholinesterase inhibition

Coptis species extract is high in berberine, and its n-butanol fraction shows significant inhibitory activity against acetylcholinesterase (AChE), especially from *C. teeta* extract and when mixing extracts from different herbs used in traditional Chinese medicine (TCM) [Kong et al. 2019, Qi et al. 2022, Tan et al. 2022]. The use of AutoDock software to simulate the interaction of berberine with target proteins in the treatment of Alzheimer's disease indicated the binding of berberine in the peripheral anionic site (PAS) of AChE through three types of bonds [Li et al. 2019, Wang et al. 2022]. The binding occurs through hydrophobic, hydrogen and π-stacking interactions [Kong et al. 2019, Qi et al. 2022]. This correlates with evidence of AChE inhibition by berberine through non-competitive interaction [Kong et al. 2019, Li et al. 2019, Sobolova et al. 2020, Adefegha et al. 2021, Tuzimski and Petruczynik 2021, Raghuvanshi et al. 2023]. The introduction of sulfonyl groups increases the inhibitory potential significantly more than the substitution of carbonyl groups [Raghuvanshi et al. 2023]. Berberine inhibits AChE more strongly than galantamine but weaker than donepezil – cholinesterase inhibitors used in the treatment of AD [Amat-Ur-Rasool et al. 2021a, 2021b]. This effect can be enhanced by combining berberine with galantamine or tacrine [Amat-Ur-Rasool et al. 2021b]. Butyrylcholinesterase is also inhibited after the administration of berberine or its derivatives [Sobolova et al. 2020, Adefegha et al. 2021, Raghuvanshi et al. 2023]. Another form of berberine delivery is the creation of nanoliposomes or other nanoparticles, which, especially after modification with lactoferrin, have an inhibitory effect on AChE [Singh et al. 2021, Wang et al. 2023].

Reduction of oxidative stress

Berberine reduces the level of reactive oxygen species (ROS) in cells exposed to the toxic effects of Aβ by inhibiting the expression of the nuclear transcription factor NF kappa B (NF-κB) through the reduction of p65 phosphorylation [Zhao et al. 2019, Rad et al. 2022, Zhang et al. 2023]. This reduces the rate of lipid peroxidation, such as malondialdehyde, which is a marker of oxidative stress, and the intensity of protein oxidation [Rajasekhar et al. 2020, Adefegha et al. 2021, Liang et al. 2021, Singh et al. 2021]. Berberine also increases the concentration of catalase and superoxide dismutase, which have antioxidant properties, especially in combination with curcumin [Lin et al. 2020, Singh et al. 2021]. In addition, berberine reduces the potential of Aβ to produce ROS by binding to Cu^{2+} associated with Aβ, but the durability of this effect is dependent on the use of naturally occurring substances [Rajasekhar et al. 2020]. Berberine normalises the morphology of the endoplasmic reticulum and reduces the concentration of immunoglobulin-binding protein (BiP), which belongs to heat shock proteins, whose increase indicates ongoing oxidative stress in the reticulum [Liang et al. 2021, Wu et al. 2021]. The reduction of oxidative stress levels caused by berberine leads to a decrease in the phosphorylation of the eIF2α protein, which regulates the expression of BACE-1 [Liang et al. 2021, Wu et al. 2021]. Berberine has an effect on ROS production, but it does not have any effect on radicals that have already been produced and does not protect DNA from damage caused by them [Rajasekhar et al. 2020].

Anti-inflammatory effect

Berberine has an anti-inflammatory effect on the inflammatory process occurring in brain tissue exposed to mutations in the presenilin-1 and Aβ genes. It reduces the concentration of IL-1β, IL-6 and TNF-α [Xu et al. 2018, Lin et al. 2020, Guo et al. 2021, Wong et al. 2021, Yang and Wang 2022], which may occur as a result of circHDAC9 stimulation [Zhang et al. 2020] or by an increase in miR-107 expression inducing inhibition of ZNF217 protein activity [Wang and Jin 2019]. It reduces the concentration of prostaglandin E2 by decreasing the expression of cyclooxygenase-2, which has a pro-inflammatory effect and is involved in the pathogenesis of memory disorders [Xu et al. 2018]. On the contrary, it increases the concentration of prostaglandin C-1α, which has anti-inflammatory and antioxidant effects [Yang and Wang 2022]. Another mechanism influencing the reduction of pro-inflammatory cytokine concentrations is the reduction of induced nitric oxide synthase (iNOS) expression by increasing the expression of the SOCS1 suppressor in microglia [Guo et al. 2021]. The suppression of NOS1 expression occurs through the action of miR-188 [Chen et al. 2020]. These are enzymes responsible for the synthesis of nitric oxide, which enhances the synthesis of pro-inflammatory prostaglandins and ROS, and for the synthesis of the cytokine signalling suppressor [Hernández et al. 2019, Singh et al. 2021]. However, berberine does not exhibit NO binding and inactivation properties, and this effect is not enhanced in the presence of H_2O_2 [Rajasekhar et al. 2020]. Berberine may also modulate the inflammatory response by binding to the peroxisome proliferator-activated receptor γ (PPARγ), whose activity results in the attenuation of inflammation [Wong et al. 2021], and by inhibiting prolyl endopeptidase (POP) [Sobolova et al. 2020].

Apoptosis

The use of berberine reduces the percentage of apoptotic cells despite the toxic effects of Aβ [Wang and Jin 2019, Chen et al. 2020, Ge et al. 2020, Rajasekhar et al. 2020, Zhang et al. 2020, Liang et al. 2021, Zhang et al. 2023]. This is confirmed by the reduced LDH concentration after its use [Xu et al. 2018, Ge et al. 2020]. In the AD model, there is an increase in caspase-3 and -9 activity in the hippocampus [Rajasekhar et al. 2020, Wang et al. 2023]. The use of berberine, also in the form of a solution or nanoliposomes, reduces the activity of these enzymes by increasing the expression of Bcl-2 and decreasing the expression of Bax, as well as regulating the concentrations of proteins promoting caspase activation, such as Cyt C [Chen et al. 2020, Ge et al. 2020, Rajasekhar et al. 2020, Liang et al. 2021, Rad et al. 2022, Wang et al. 2023, Zhang et al. 2023]. This appears as a decrease in chromatin aggregation and karyopyknosis [Zhang et al. 2023]. The result is an increase in the number of cells containing Nissl bodies, which decrease during the progression of the disease due to neuronal damage [Yang and Wang 2022]. Another important mechanism for preventing apoptosis of cells exposed to Aβ is the effect of berberine on miR-188. It reverses the toxic effects of Aβ by increasing the concentration of miR-188, which reduces the concentration of caspase-3 and slows down the rate of apoptosis [Chen et al. 2020]. It also increases the concentration of circHDAC9 and the level of miR-132-3p, which is involved in anti-apoptotic activity [Ge et al. 2020, Zhang et al. 2020].

Influence on neuronal cells

Aβ reduces the viability of neuronal cells, damages their morphology and reduces the number of synaptic connections [Zhao et al. 2019, Zhang et al. 2023]. These abnormalities

are reversed by berberine, with an optimal concentration of 1 μM or a dose of 30 ppm, and a possible mechanism is the promotion of circHDAC9 expression, which reduces the concentration of miR-142-5p [Xu et al. 2018, Wang and Jin 2019, Zhao et al. 2019, Rajasekhar et al. 2020, Zhang et al. 2020, Rad et al. 2022, Zhang et al. 2023]. The use of berberine reduces the permeability of the cell membrane to Aβ, which reduces cellular toxicity [Rajasekhar et al. 2020]. Berberine also stimulates the release of neurotrophic factors such as brain-derived neurotrophic factor (BDNF) and glial-derived neurotrophic factor (GDNF) by increasing SOCS1 expression, which may lead to an increase in the number of neuronal cells [Guo et al. 2021]. In addition, berberine has a reparative effect on nerve cell damage [Sun et al. 2025]. Berberine therapy causes a decrease in the concentration of markers of damage and activation of glial cells such as glial fibrillary acidic protein (GFAP) and ionised calcium-binding molecule-1 (IBA1) [Lin et al. 2020]. Moreover, at concentrations of 3 μM, it affects the metabolic profile of cells exposed to Aβ, enabling its normalisation, especially with regard to the levels of acetic acid, d-fructose, L-glutamic acid, glutathione, L-lactic acid and pyroglutamic acid metabolites [Wong et al. 2021]. Berberine also increases the efficiency of ATP production in the mitochondria of hippocampal neurons, which has been reduced by the toxic effects of Aβ [Zhao et al. 2019]. The reason for this is an increase in the reduced density of mitochondria in neurons, an increase in their size and improved mobility. On the other hand, berberine enhances cell autophagy by increasing 5'AMP-activated kinase signalling [Lin et al. 2020].

Research on the effect of berberine on memory functions has also included studies on animal models. Enriching the diet of mice with berberine increased learning abilities and memory functions during the Morris Water Maze Test [Sun et al. 2025].

SUMMARY

Berberine has been used for medicinal purposes since ancient times, as evidenced by numerous accounts in traditional medicine. Extensive research on its properties reveals a wide range of potential applications. Neurodegenerative diseases, which are a significant social problem, may be another possible indication for the use of berberine due to its multifaceted therapeutic effects. Despite promising preclinical results, further experiments involving biological models are necessary to comprehensively assess the efficacy, safety, and potential therapeutic and adverse effects of berberine before it could be introduced into clinical practice. Although berberine has been tested in human clinical trials, these studies have focused on other medical conditions such as hypercholesterolaemia and intestinal microflora disorders. For the evaluation of the practical treatment of Alzheimer's disease with berberine, it is required to conduct clinical trials in people also for this indication, after prior assessment of the safety profile.

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