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REVIEW ARTICLE

Berberine: A Plant-derived Alkaloid with Therapeutic Potential to Combat Alzheimer's disease

Anurag K. Singh[1], Santosh K. Singh[1], Manmath K. Nandi[2], Gaurav Mishra[2], Anand Maurya[2], Arati Rai[3], Gopal K. Rai[4], Rajendra Awasthi[5,*], Bhupesh Sharma[6] and Giriraj T. Kulkarni[5]

[1]*Centre of Experimental Medicine & Surgery, Institute of Medical Sciences, Banaras Hindu University, Varanasi-221005, Uttar Pradesh, India;* [2]*Institute of Medical Sciences, Faculty of Ayurveda, Department of Medicinal Chemistry, Banaras Hindu University, Varanasi, 221005, Uttar Pradesh, India;* [3]*Hygia Institute of Pharmaceutical Education & Research, Lucknow-226020, Uttar Pradesh, India;* [4]*Department of Pharmaceutical Engineering & Technology, Indian Institute of Technology (Banaras Hindu University), Varanasi-221005, Uttar Pradesh, India;* [5]*Department of Pharmaceutics, Amity Institute of Pharmacy, Amity University Uttar Pradesh, Sec 125, Noida, 201303, Uttar Pradesh, India;* [6]*Department of Pharmacology, Amity Institute of Pharmacy, Amity University Uttar Pradesh, Sec 125, Noida, 201303, Uttar Pradesh, India*

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Abstract: Berberine (a protoberberine isoquinoline alkaloid) has shown promising pharmacological activities, including analgesic, anti-inflammatory, anticancer, antidiabetic, anti-hyperlipidemic, cardioprotective, memory enhancement, antidepressant, antioxidant, anti-nociceptive, antimicrobial, anti-HIV and cholesterol-lowering effects. It is used in the treatment of the neurodegenerative disorder. It has strong evidence to serve as a potent phytoconstituent in the treatment of various neurodegenerative disorders such as AD. It limits the extracellular amyloid plaques and intracellular neurofibrillary tangles. It has also lipid-glucose lowering ability, hence can be used as a protective agent in atherosclerosis and AD. However, more detailed investigations along with safety assessment of berberine are warranted to clarify its role in limiting various risk factors and AD-related pathologies. This review highlights the pharmacological basis to control oxidative stress, neuroinflammation and protective effect of berberine in AD, which will benefit to the biological scientists in understanding and exploring the new vistas of berberine in combating Alzheimer's disease.

Keywords: Alzheimer's disease, berberine, amyloid, tau, oxidative stress, neuroinflammation, neurodegenerative disorder.

1. INTRODUCTION

The Alzheimer's Disease (AD) is a slowly progressing disease causing irreversible destruction of brain cells, which are responsible for the storage and processing of information. This leads to the consequent deterioration of thinking ability and memory [1]. AD is a neurodegenerative type of dementia, which starts mild and gets progressively worse. According to Alzheimer's Disease International, dementia due to AD is the most common form which has affected 44 million people worldwide. The estimated number of new AD cases in 2050 will be approx. 135 million [2]. Neurodegenerative dementia caused by AD is characterized by progressive cognitive decline and its unique pathology [3, 4]. In 1906, Alois Alzheimer reported the first case of intellectual deterioration with the histological findings of senile plaques and neurofibrillary tangles in the patient Auguste Deter. Alzheimer discussed his clinical findings in the 37th Summit of South-West German Psychiatrists in Tubingen [5]. AD presents with an insidious decline in memory that progresses to affect language, visuospatial perception, calculations, and executive functioning. Behavioral and psychiatric symptoms are also frequent in AD [6]. It can be diagnosed clinically, as no laboratory tests are available to confirm AD. Neuritic plaques and neurofibrillary tangles are the neuropathologic hallmarks of AD. Currently, available therapies have demonstrated modest benefits, but likely do not alter disease progression. Caregivers play a key role in managing patient health and quality of life and should be encouraged to seek out daycare centers, home health services, respite care, and additional social support. When brain cells degenerate and

*Address correspondence to this author at the Department of Pharmaceutics, Amity Institute of Pharmacy, Amity University Uttar Pradesh, Sec 125, Noida, 201303, Uttar Pradesh, India; Tel: +91-9459234530;
E-mail: awasthi02@gmail.com

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die, the brain markedly shrinks in some regions. The person with Alzheimer's disease has less brain tissue than a normal person. This shrinkage continues over time and affects brain functioning. The atrophy can be marked in the brain of a patient with extended sulci and shrinkage of the gyri.

Currently, available pharmacotherapy is principally symptomatic with transitory clinical benefits in terms of cognition and behavioral appearance of the disease. Drachman and Leavitt suggested a correlation of memory with the cholinergic system and reported the age-dependent degradation of memory [7]. In the same time frame, two independent British groups revealed the association of AD pathology with a severe loss of central cholinergic neurons; more specifically the degree of cholinergic loss in the nucleus basalis of Meynert [8, 9]. Even after extensive developments in the understanding of the disease, we are still not aware that why and how it starts and progresses. All the treatment approaches are hypothetical which still need to be approved. Hence, it remains a highly debatable topic in pharmaceutical research and in clinical practice. Therefore, we neither have a cure for Alzheimer's disease nor its progression can reverse. However, the present treatment options and lifestyle choices can often significantly control the progression of the disease. It is hypothesized that AD (cholinergic disorder) is similar to Parkinson's disease (dopaminergic disorder) [10].

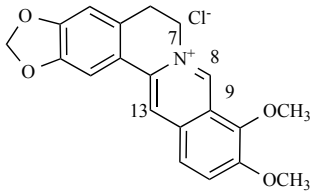

Fig. (1). Chemical structure of berberine [5,6-dihydro-9, 10-dimethoxybenzo (g)-1,3-benzodioxolo (5,6-a) quinolizinium].

2. BERBERINE

Berberine (molecular formula, $C_{20}H_{19}NO_5$ and molecular weight, 353.36 g/mol) is the principal isoquinoline alkaloidal (Fig. **1**) constituent of stems and roots of various Berberis species such as *B. aristata* [11], *B. petiolaris* [12] and *B. vulgaris* [13]. *B. aristata* contains about 5% berberine in the roots and 4.2% in the stem [14]. A high yield of berberine has been reported in *B. darwinii* [15, 16]. Other berberine containing plants are *Argemone mexicana* (prickly poppy), *Coptis chinensis* (Chinese goldthread), *Camellia japonica*, *Coptis teeta* (rhizome 8-9%), *Eschscholzia californica* (Californian poppy) and *Hydrastis canadensis*, *Mahonia aquifolium*, *Tinospora cordifolia*, *Xanthorhiza simplicissima* (yellow root), and *Phellodendron amurense*. High level of berberine content has been reported in *Phellodendron amurense* (4%) and *Callosobruchus chinensis* (8%). Berberine is yellow or orange crystalline powder, which has a faint characteristic odor or odorless and characteristic bitter-taste. It is extracted by alcohol in the neutral medium or with the addition of acetic acid. It is slightly soluble in ethanol, sparingly soluble in methanol and slightly soluble in water. Apparent permeability co-efficient of berberine across the intestinal tissue is very small ($\approx 10^{-7}$ cm/s). P-gp expression in intestinal cells and CYP 450-dependent first-pass metabolism are the major cause of its poor absorption.

2.1. Therapeutic Applications of Berberine

Berberine has wide application in traditional Ayurvedic and Chinese medicine systems [17]. It has shown promising pharmacological activities, including analgesic [18], anti-inflammatory [19-21], anticancer [22-25], antidiabetic [26, 27], anti-hyperlipidemic, cardioprotective [28], memory enhancement, antidepressant [29-31], antioxidant [32], anti-nociceptive [33], antimicrobial [34], anti-HIV [35] and cholesterol-lowering [36, 37] effects. It has been also used in the treatment of neurodegenerative disorders [19, 22, 27, 38-43], rheumatoid arthritis, irritable bowel syndrome, osteoporosis, respiratory disorders [17], obesity, and atherosclerosis [44]. Berberine has been reported to inhibit vascular smooth muscle cell migration through suppressing the activation of the PI3 K/Akt pathway and subsequent expressions of matrix metalloproteinase [45]. It inhibits the growth of cancer cells, promotes apoptosis of tumor cells, induces tumor cell differentiation and suppresses tumor cell metastasis [46]. The potential use of berberine in the treatment of chronic congestive heart failure and diabetes has been well-documented [47-51]. It also plays an important role in the treatment of hypercholesterolemia (*i.e.* serum triglycerides, cholesterol, and low-density lipoprotein) [43, 52, 53]. Neuroprotective role of berberine to improve survival, development, neurons functioning and protecting the electrically excitable brain cells has been reported [54]. Hence, it has strong evidence to serve as a potent phytoconstituent in the treatment of various neurodegenerative disorders such as AD [55, 56], Parkinson's disease [57] and Huntington's disease [58].

Recently, Zou *et al*. reported improved artificially induced brain ischemia (induced by permanent occlusion of the middle cerebral artery) and behavioral functional impairment by berberine [59]. Berberine mediated neuroprotection is related to Akt/GSK3β/ERK1/2 survival/apoptotic signaling pathway, Jun amino-terminal kinases (JNK) and Caspase-3 activity inhibition [60, 61]. It has beneficial effect on stroke [62-64] and neurodegenerative and neuropsychiatric disorders [19, 55, 58, 60, 65, 66]. Hence, it has been widely investigated as a second-generation anti-AD drug acting as acetylcholine esterase inhibitor with positive outcomes in stroke [62-64]. This is further supported by a computational screening of synthetic molecules, dietary phytochemicals, which results in reduced levels of acetylcholine neurotransmitters [56]. Thus, berberine could be a potential drug template to develop more effective anti-AD agents [67, 68].

3. AD-RELATED HYPOTHESIS AND THE POSSIBLE ROLE OF BERBERINE

3.1. Symptomatic Hypothesis

3.1.1. Cholinergic Hypothesis

Cholinergic hypothesis states that AD arises due to the deficiency of acetylcholine level. The early therapeutic approach was based on the cholinergic hypothesis, including

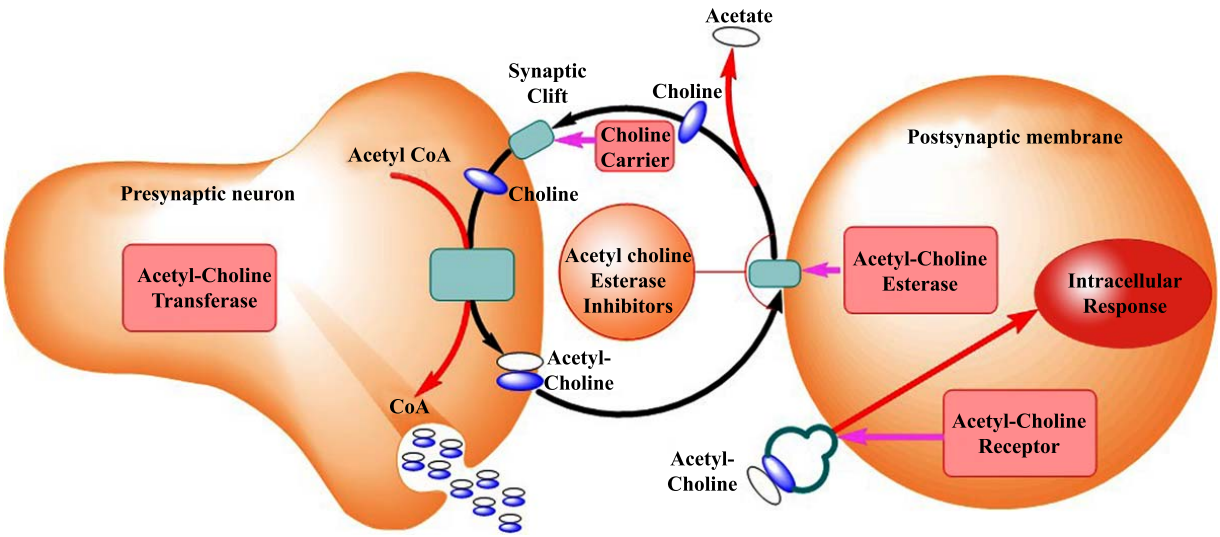

Fig. (2). Schematics diagrammatic fabrication mechanism of ACh through the presynaptic neuron and postsynaptic membrane. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

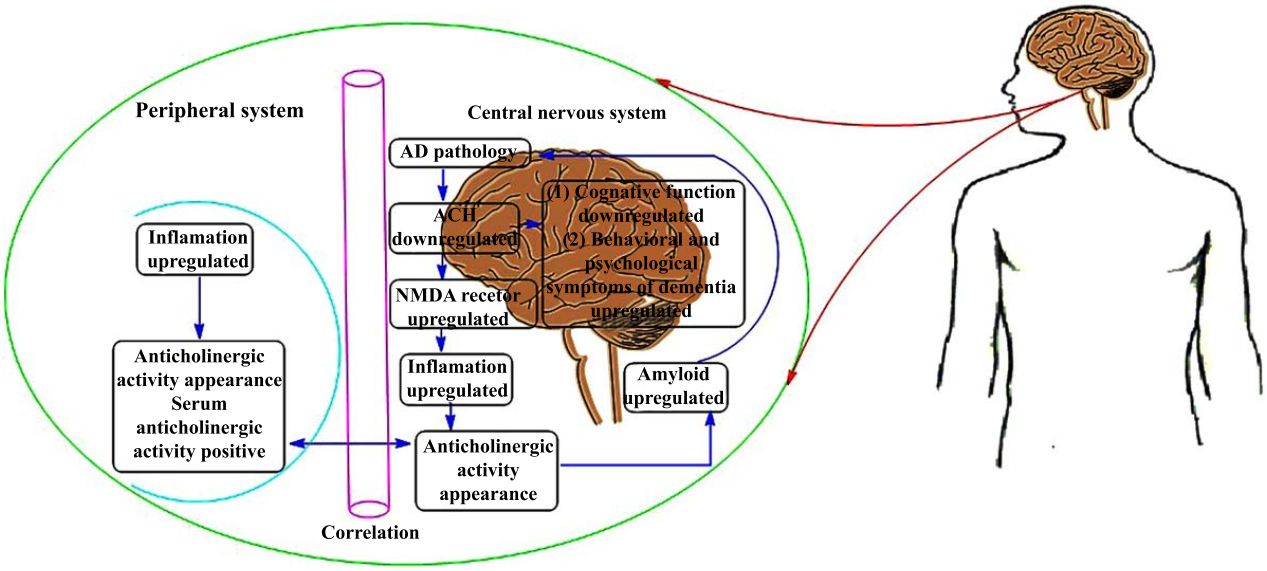

Fig. (3). Effect of decreased Acetyl Choline (ACh) level or Ach receptor sensitivity on cognitive dysfunction, behavioral and psychological symptoms of dementia, and anticholinergic activity due to the inflammation in the central and peripheral nervous systems. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

restoration of cholinergic nuclei (Fig. **2**). The cell-replacement therapy has been investigated on the basis of cholinergic hypothesis. All first-generation anti-AD drugs preserve acetylcholine by inhibiting acetylcholinesterase enzyme (AChE). These drugs can only treat the disease symptoms, but they neither halt nor reverse it. This suggests that along with the acetylcholine deficiency, widespread brain tissue damage may also be the cause of AD. Thus, cell replacement therapies are likely to be impractical. Cholinergic effects are also identified as a potential causative factor for the formation of plaques and tangles [69], which leads to generalized neuroinflammation [70].

Acetylcholine degradation not only causes cognitive dysfunction, behavioral and psychological symptoms of dementia but also induces inflammation in the central and peripheral nervous systems, which causes anticholinergic activity in both the systems through cytokine pathways. Anticholinergic activity increases amyloid pathology and decreases acetylcholine level, which is known as endogenous anticholinergic activity cascade (Fig. **3**) [71].

3.1.2. Berberine and Cholinergic Pathology

Ellman's coupled enzyme assay confirmed dose-dependent inhibition of AChE (IC_{50} (mM) values of 1.85) by berberine extracted from the aerial portion of *Chelidonium majus* L. when compared to the standard anti-dementia drug (tacrine) (IC_{50} (mM) value of 0.12). Berberine exhibited selective inhibition for AChE (from electric eel) compared with horse serum Butylcholinesterase's Enzyme (42.6), while tacrine had low selectivity (0.05) [72]. Similar results have been reported for galantamine [32, 73-75] and crude ethanolic extract of *Berberis vulgaris* [76]. Berberine leads

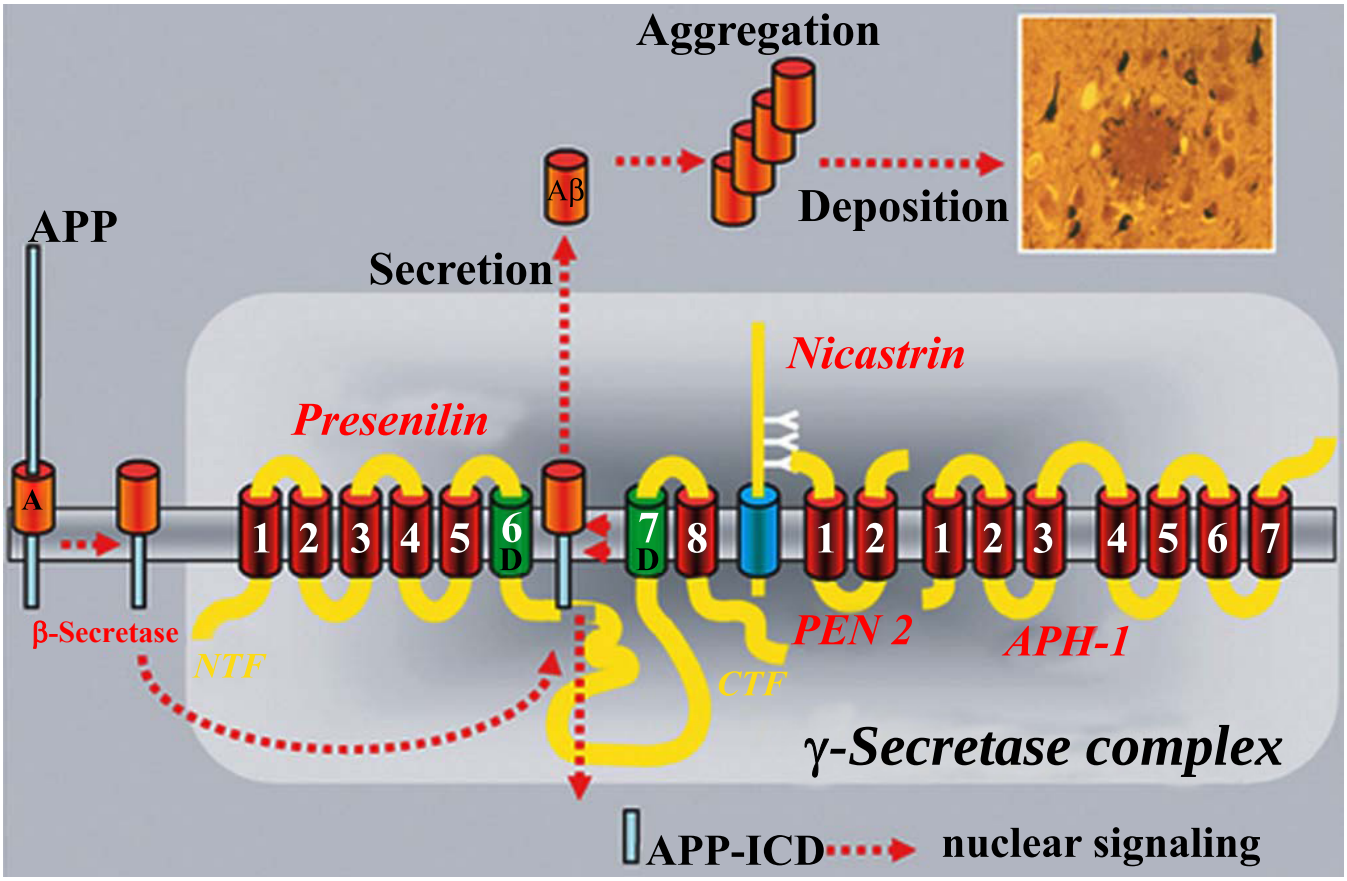

Fig. (4). Schematics presentation of the generation of Aβ through APP *via* proteolytic processing by β- and γ-secretase (Reused with permission [91]). *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

to the conformational change in the active site and increases entropy due to the nonreversible blockage of the active site. An *in-silico* approach has been introduced to examine the potential of AChE inhibitor as anti-Alzheimer drug [56]. Zhaoa *et al*. carried *in-vitro* AChE inhibition assay of AChE inhibitor isolated from *Coptis chinensis* Franch using microplate reader. The concentration of berberine required to inhibit 50% (IC_{50}) was 141.8 μM [77].

3.2. Disease-Modifying Hypothesis

3.2.1. β-Amyloid Hypothesis

Amyloid cascade hypothesis is widely explored to develop AD therapeutics [78]. The pathophysiological mechanism converts soluble Aβ peptides into insoluble fibrils *via* fibrillary oligomers. These fibrils accumulate extracellularly in neural tissues, intima of the brain and systemic vessels [79]. This extracellular accumulation of Aβ oligomers and fibrils cause a neuronal loss in AD progression *via* synaptic dysfunction followed by affected axons and dendritic spines [80-83]. Besides these changes, the toxic Aβ species also trigger secondary pathological processes *via* oxidative stress and inflammation, which accelerates neuronal deterioration, dysfunction and death [84, 85]. Intracerebral amyloidosis is one of the preliminary pathological changes which starts many years before the onset of clinical symptoms in the brain of individuals with AD [86, 87]. β-amyloid hypothesis is supported by the identical clinical and pathologic phenotype among the sporadic late onset of AD and inherited early onset form of AD (results from autosomal dominant mutations to the amyloid precursor protein (APP) genes and two subunits of λ secretase presinilin 1 and 2) (Fig. **4**) [88-91].

3.2.2. Berberine and β-Amyloid Pathology

β-amyloid (Aβ), a typical pathological emblem, is the result of abnormal casting of APP. Physiological generation of Aβ resulted from succulent APP proteolysis is responsible for the progression of AD [92-94]. Generation of Aβ from sequential APP proteolysis can be categorized into two physiological pathways, namely amyloidogenic and non-amyloidogenic [95, 96]. The amyloidogenic pathway is mediated by β-secretase which cleaves the APP and generates soluble peptide APPβ (sAPPβ) and C-99 fragment (C-terminal fragment) which further cleaves into Aβ and APP intracellular domain. The non-amyloidogenic pathway is mediated by the breakdown of APP catalyzed by α-secretase into a soluble fragment of APP (sAPPα) and C-terminal fragment (C-99). C-99 is further cleaved in p3 peptide and APP intracellular domain by γ-secretase (Fig. **5**) [97-99].

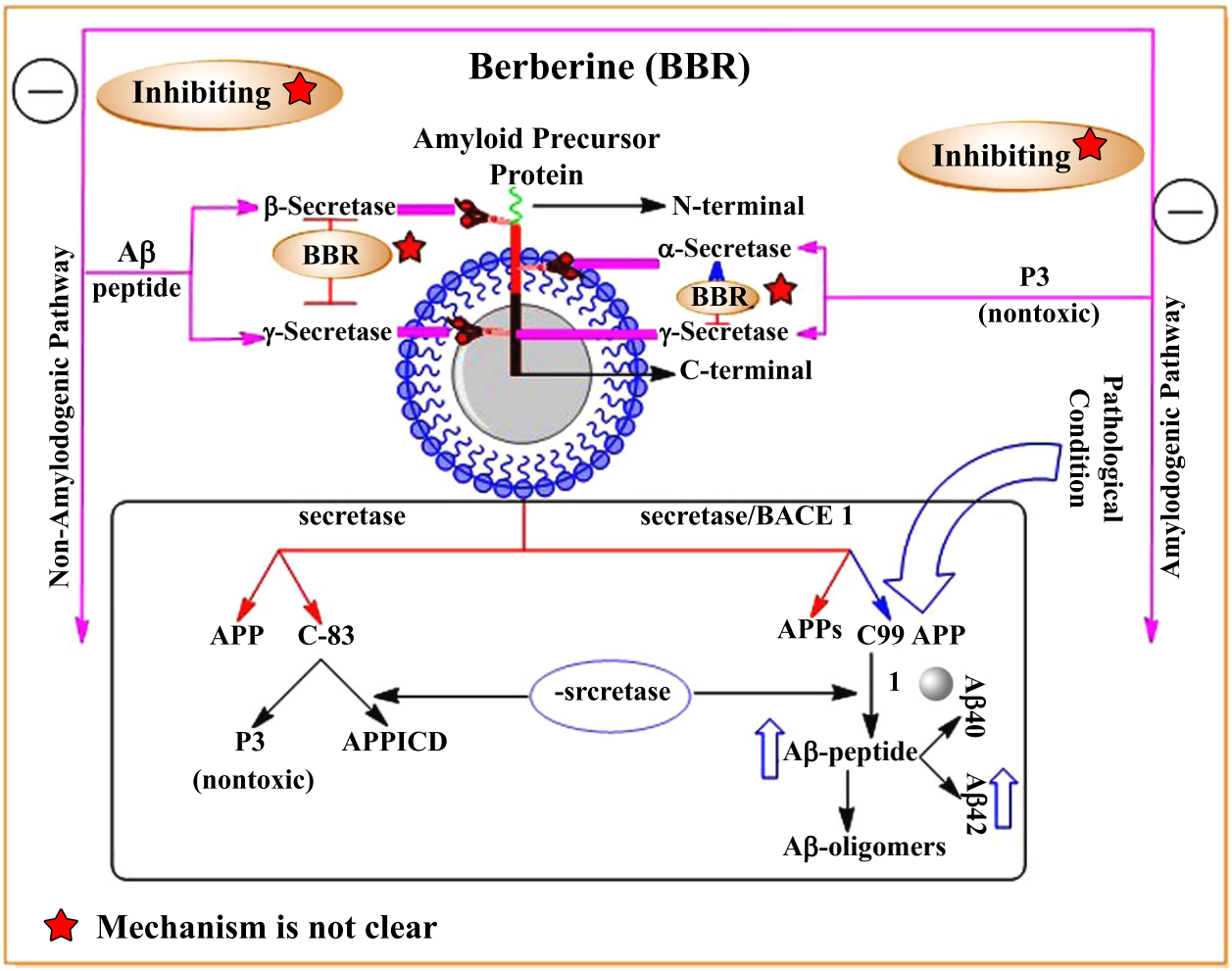

Fig. (5). Schematic representation of APP processing pathways and promising mechanisms by which berberine (BBR) alters the metabolism of APP-BBR obstruct the process of the amyloidogenic pathway and could decline β-secretase and γ-secretase, pull down the Aβ release and the construction of APP. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

Therapeutic benefits of berberine in the treatment of AD may be due to the decline of Aβ production [100, 101]. Berberine restricts the mitogen-activated protein kinase signaling pathway in primary microglia and BV2 cells by inhibiting Aβ-intensified production of interleukin-6 and monocyte chemotactic protein-1. It down-regulates cyclo-oxygenase-2 expression and induce nitric oxide synthase by blocking phosphoinositide 3-kinase/protein kinase β [102]. *In-vivo* study in AD transgenic mouse models explained the role of berberine in ameliorates Aβ pathology, gliosis and cognitive impairment [103]. Intragastric administration of berberine in rabbits decreased hippocampus degeneration, changed behavior, and deregulated the β-site APP cleaving enzyme-1 (BACE-1) [104, 105]. Asai *et al.* reported therapeutic benefits of berberine in Aβ reduction by APP processing modulation in human neuroglioma H4 cells with no evidence of cellular toxicity [106]. Further, Jung *et al.* [107] and Zhu *et al*. [108] reported berberine induced deactivation of ERK1/2 pathway (up-regulates BACE expression) in HEK293 cells. However, the mode of action of berberine in Aβ down regulation is not clear. Berberine has the ability to cross BBB and possess multiple pharmacological and therapeutic activities, including neuroprotective and neurotrophic effects [19, 109, 110]. The literature suggests that berberine would be a favorable candidate for altering APP breakdown *via* modifiable APP processing or Aβ clearance.

3.3. Tau and Neurofibrillary Tangles

Intracellular neurofibrillary tangle (NFT) is the subsequent pathological emblem of AD. NFT is the part of microtubule-associated protein tau [111]. In contrast to the axon-specific expression of tau in developing healthy neurons, hyper-phosphorylated tau is translocated to the somato-dendritic section in AD [112]. Phosphorylation of tau is critical to its function. Hyper-phosphorylated tau proteins form paired helical filaments [113]. This leads to the neuronal injury and cell death *via* flimsiness of microtubules and interruption of axonal transport. Thus, the elevated level of total or phosphorylated tau in CSF could be a strong sign for neuronal injury/degeneration [114]. A strong link has been evidenced between NFT and topography. Clinical phenotype NFTs could not be developed or successfully targeted for the treatment of neurodegenerative disorders [115]. Tau targeting therapies minimize, stabilize or inhibit hyper-phosphorylation or aggregation of the protein (Fig. **6**).

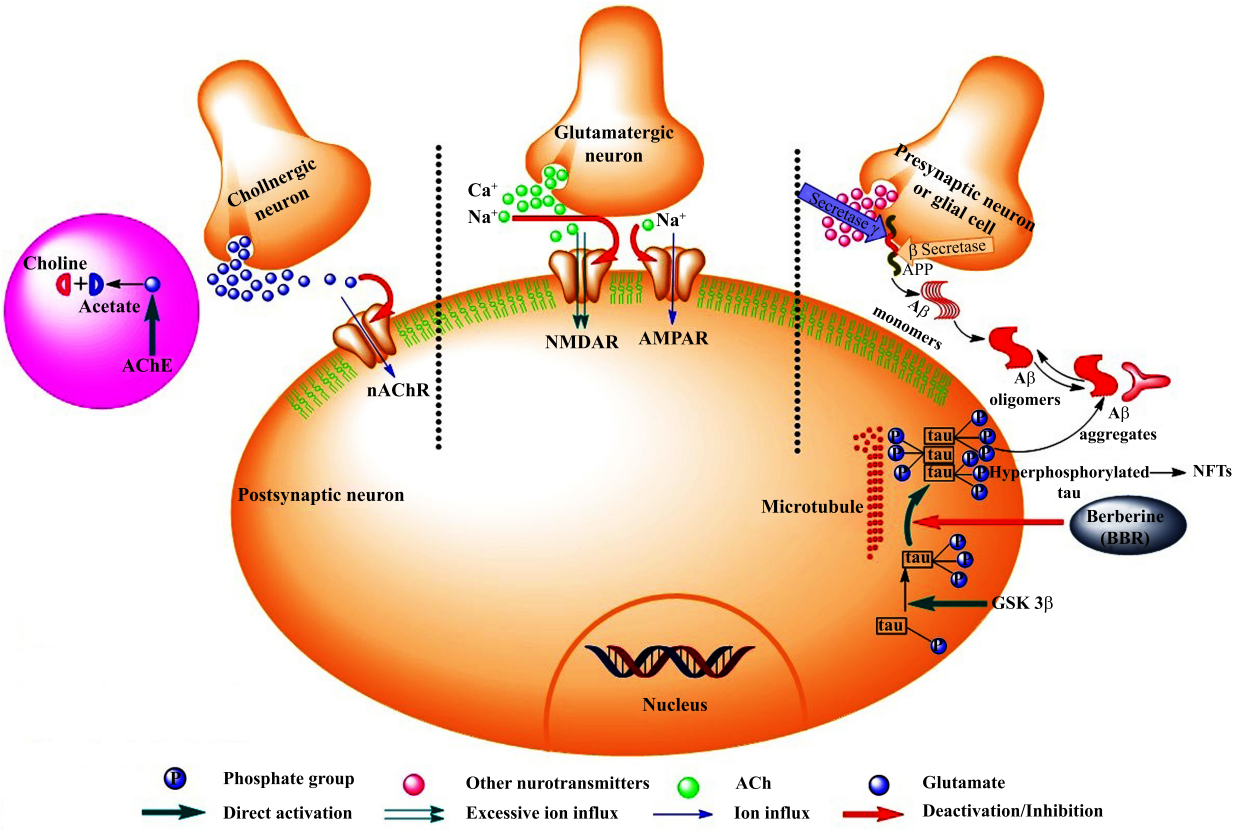

Fig. (6). The proposed molecular mechanism behind the inhibition of hyperphosphorylated tau and neurofibrillary tangle (NFTs) formation. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

3.3.1. Berberine and Tau Pathology

NFTs are extremely phosphorylated microtubule related tau protein and disrupt axonal transport. Hence, the NFTs and toxic soluble tau are generated which are typical neuropathological bruise of AD. Axonal transport in neuroblastoma-2a cells could be diminished by berberine dependent tau hyperphosphorylation and Calyculin A-induced cytotoxicity [116]. Berberine is effective in reducing Calyculin A-induced tau hyperphosphorylation at Ser 198/199/202, Ser 396, Ser 404, Thr 205, and Thr 231. It also helps to resume 2A activity of protein phosphates and limit glycogen synthase kinase-3 beta (GSK-3β) by phosphatase activity assay and GSK-3β phosphorylation at Tyr 216 and Ser 9 of tau [117]. The exact mechanism of tau hyperphosphorylation reduction still needs to be explored. Berberine diminishes the hyperphosphorylation by limiting the Aβ mediated degradation of hyperphosphorylated tau (Fig. **6**).

3.4. Berberine Inhibits Oxidative Stress in AD

Oxidative stress *via* multifunctional pathway plays crucial role in pathology and progression of AD. Berberine is reported to regulate neurotransmitter, neuroinflammation, and oxidative stress. It is also effective in neuro-metabolism and other multi-target pathways. Thus, it could have a crucial role in senile dementia treatment. It has been hypothesized that berberine can act as neuroprotective by attenuating oxidative stress in AD pathogenesis and hence could be potential for AD treatment [118]. Oxidative stress plays a key role in AD progression by triggering an active and self-propagating cycle with chronic neuroinflammation. This leads to unalterable neuronal dysfunction and cell death [85]. It is assumed that oxidative stress in AD *via* synapse destruction lead to cognitive impairment and dementia [4]. Oxidative stress may up-regulate the β and γ-secretase, which lead to the production of Aβ by two consecutive cleavages of APP. The accretion of Aβ and may lead to the oxidative and neuroinflammatory processes to the formation of NFTs result various cycles between Aβ pathology and oxidation. Berberine is effective in various neuro disorders and other inflammations because of its ability to check the oxidative stress and related processes [66, 76, 118-122]. It regulates various inflammatory factors, including up and down regulation of GPx and CuZn-superoxide dismutase, elevate potential which improves the oxidant-antioxidant balance and inhibit the activation of RhoA/ ROCK signaling. It plays a key role in diabetes treatment, lipid-lowering and limiting serum cholesterol, triglycerides, and cholesterol associated with partial mitochondrial oxidation [122-135].

3.5. Neuroprotection/ Neurotrophic Support in the AD of Berberine

Neuroprotective or neurotrophic statements make sure that the cells are healthy even in disease-specific pathologic condition. Reduction of inflammation or other downstream markers of AD pathobiology can be incorporated under this

category [136-139]. The mechanisms of reduction of AD progression are not yet clear, but the cholesterol-lowering and anti-inflammatory properties have been found to be useful in treating AD. The reduction of Aβ by these agents has been reported earlier [140]. However, randomized placebo-controlled studies of NSAIDs have failed so far [141-143]. Similarly, mixed results have been obtained with statins. The religious orders study [144] and cardiovascular health study [145, 146] reported that the statins are non-effective in AD. On the other side, the reduced burden of NFT in patients using statin has been reported [147]. Jones *et al*. [148] accomplished a prospective clinical trial of donepezil and atorvastatin but could not succeed to show significant drug-placebo variance [148].

3.6. Berberine Retards Inflammation

Berberine may obstruct the progression of inflammation, which is one of the most significant pathological sign of various diseases. It has broad-spectrum antimicrobial activity, which exerts shielding effect over numerous experimental models by obstructing the advancement of inflammations such as obesity, diabetes mellitus, heart diseases, cancers, hypertension and cerebral ischemia [149].

3.6.1. Berberine Alleviates Neuroinflammation in AD

Extensive literature outcomes have pointed out the therapeutic potential of berberine in neurodegenerative disorders by slowing down the evolution of neuroinflammation because of its anti-inflammatory activity in AD [19, 30, 66, 102, 135]. Tau hyperphosphorylation and Aβ accumulation are the motivating factors of neuroinflammation in the brain [30, 150-156]. Zhu and Qian [157] reported that berberine might exaggerate the inflammatory pathology in the rat model of AD. This was established by injecting Aβ into the rat's hippocampus bilaterally and intragastric administration of berberine chloride (50 mg/kg). This ameliorates the spatial memory impairment and increases the expression of IL-1β and inducible nitric oxide synthase. The pharmacological activities of berberine related to AD hypothesis are tabulated in Table **1**.

Berberine exerts a great impact on neuronal regeneration, neuroprotection, neuritis outgrowth, and axonal myelination or remyelination, as depicted from the previously reported studies (Table **2**). Thus, it can be a potential candidate for the treatment of neurodegenerative diseases.

4. RISK FACTORS

Some commonly associated disease symptoms of AD are not seen so often in people without the disorder. AD may have a direct link with these factors. Examples of preventable or modifiable factors are reducing the risk of diabetes or heart disease which may, in turn, cut the risk of dementia. Risk factors associated with Alzheimer's disease include:

4.1. Unavoidable Risk Factors

Age is an important risk factor for disorders. It is more likely in individuals over 85 years of age [83]. Genetic inheritance is also a significant factor associated with higher risk of AD. This is the second most prominent risk factor after age. Individuals having gene like apolipoprotein E or ApoE have three to eight times more risk of AD depending on their specific genetics [173]. Females are more affected with AD than males [174]. Cardiovascular problems are growing evidence that supports a strong and likely causal association between Cardiovascular Disease (CVD) and its risk factors with an incidence of cognitive decline and AD. Individuals with subclinical CVD are at higher risk for dementia and AD. Cardiovascular risk factors also associated with dementia, including hypertension, high Low Density Lipoprotein (LDL) cholesterol, low High Density Lipoprotein (HDL) cholesterol and diabetes. Epidemiological evidence strongly supports an association between type 2 diabetes and AD [146]. Based on prospective studies, it has been reported that the relative risk of dementia is 1.6 (95% CI 1.4-1.8) when compared to those with and without type 2 diabetes [146, 175].

4.2. Potentially Avoidable or Modifiable Factors

Diabetes, high cholesterol level, and high blood pressure increase vascular risk. These factors also increase the risk of stroke, which can lead to another type of dementia. Low educational, occupational attainments, prior head injury, sleep disorders are modifiable or potentially avoidable factors [176].

4.3. Berberine Shrinkages the Role of Risk Factors in AD

It is well-accepted fact that all the vascular risk factors contribute to the progress of atherosclerotic vascular diseases and the formation of atherosclerotic plaque are responsible for vascular dementia and AD. Berberine can prevent the progress of atherosclerosis development [177, 178]. The antiatherosclerosis mechanism of berberine may be associated with regulating lipids, oxidative stress, inflammation, reducing blood sugar, and inhibiting vascular smooth muscle cell proliferation *via* regulating the intracellular Ca^{2+} handling of smooth muscle cells [179-183]. The model of the atherosclerotic vulnerable plaque was formed by placing a collar around the carotid artery in ApoE−/−mice treated with homocysteine thiolactone. Berberine stabilizes atherosclerotic plaque in hyperhomocysteinemia ApoE−/−mice by activating peroxisome proliferator-activated receptor gamma and inhibiting oxidative stress in endothelial cells [44]. Monocytes to endothelial cells play a crucial role during the early stages of atherosclerosis development. Berberine markedly reduces oxidized LDL-induced monocyte adhesion to human umbilical vein endothelial cells through antioxidative activation of AMP-activated protein kinase and inhibition of RhoA/Rho kinase pathway [184, 185]. Berberine decreased the expression of adhesion molecules, including VCAM1 and ICAM1. These results implicate that berberine plays a protective role in the early stages of atherosclerosis [186]. Berberine inhibits serum-induced cholesterol accumulation, vascular smooth muscle cell proliferation improves neointima formation. It also plays a potentially atheroprotective role in macrophages [187-189]. Clinically, combination therapy

Table 1. Types of neurological hypothesis with berberine and their effect on pharmacological activity.

Hypothesis	Class	Effect of Berberine on Pharmacological Activity	Enzymatic Assay/ Target Organism/ Cell Line	IC_{50}/ Inhibitory Ability in (%)	Refs.
Symptomatic hypothesis	Cholinergic pathology	Inhibited AChE in a dose-dependent manner and more selectivity towards AChE	Ellman's coupled enzyme assay	1.85 and 78.9	[72]
		In contrast to galanthamine, berberine show potent inhibitors and selectivity for AChE	Electric eel (*Electrophorus electricus*)	0.374 and 48.6	[32, 73-75]
		Berberine produces such a conformational change at the active site of AChE that increased the entropy which makes it a competitive inhibitor	Ellman's enzyme assay	% at $p < 0.05$	[76]
		The safety was studied based on computational ADME model docking	Docking study	docking score 5462	[56]
		AChE inhibition assays based on a microplate reader	*C. chinensis* Franch (Coptischinensis)	141.8	[77]
Disease-modifying hypothesis	β-amyloid pathology	Inhibited Aβ-stimulated production of interleukin-6 and monocyte chemotactic protein-1 and down-regulated the expression of cyclo-oxygenase-2 and induced nitric oxide synthase	Primary microglial and BV2 cells	--------	[102]
		Berberine ameliorates Aβ pathology, gliosis, and cognitive impairment	Transgenic mouse model of AD	--------	[103]
		Prevented the hippocampus from neurodegeneration, and lowered the activity of beta-site APP cleaving enzyme-1 (BACE-1)	Rabbit model	--------	[104]
		Reduces Aβ levels by modulating APP processing	Human neuroglioma H4 cells	--------	[106]
		Decreases the production of Aβ40/42 by inhibiting the expression of BACE *via* activation of the ERK1/2	HEK293 cells	--------	[107, 108]
Tau and Neurofibrillary tangles	Tau pathology	Berberine attenuated tau hyperphosphorylation and cytotoxicity induced by Calyculin A	Neuroblastoma-2a cells	--------	[116]
		Reduction of Calyculin A-induced tau hyperphosphorylation, and it also recovered the 2A activity of protein phosphates and limited glycogen synthase kinase-3 beta (GSK-3β)	--------	--------	[117]
Berberine inhibits oxidative stress in AD	--------	Decreasing the production of malondialdehyde and reactive oxygen species	Rat cortical neurons	--------	[135]
Neuroprotection/ Neurotrophic support in AD	--------	Nicotinamide, a class III HDAC inhibitor, improved memory	Triple transgenic mouse model of AD	--------	[158]
Berberine retards inflammation	--------	Ameliorate the spatial memory impairment and increase the expression of IL-1β and inducible nitric oxide synthase, and berberine might exaggerate the inflammation pathology	Rat model	--------	[157]

Table 2. Pharmacological activity (cell line/ *in-silico*) of berberine on the different types of disorders and their effect on targeted organism.

Effect of Berberine on Pharmacological Activity	Target Organism/ Cell Line/ *In-silico* Study	Dosage	Refs.
Binds to acetylcholinesterase, butyrylcholinesterase	Docking studies	……	[100]
Attenuates glucose neurotoxicity and promotes Nrf2-related neurite outgrowth	Cell culture system	0.1–10 nM	[26]
Axonal regeneration	Mice	20 mg/kg	[159]
Ameliorate scopolamine-induced neuronal impairment and memory dysfunction	Mice	100–200 mg/kg	[160]
Protects neurons against ischemia	Gerbil	300 mg	[161-163]
Sensitizes neurons to glutamate and rotenone injury	Mice	……	[164]
Inhibits the release of glutamate in nerve terminals from cerebral cortex	Mice	……	[64]
Neuroprotective in autoimmune encephalomyelitis	Mice	……	[165]
Antipsychotic	Mice	……	[166]
Acts as deterrent compound against feeding sugar meal of African *Anopheles gambiae*	Mosquito	……	[167]
Undergoes anti-apoptosis during hypoxia by hypoxia-inducible factor-1	Mice	……	[168]
Anti-apoptotic effect	Mice	100 mg/kg/day	[169]
Activates Nrf2 nuclear trans location and protects against oxidative damage *via* a phosphatidylinositol3-kinase/Akt-dependentmechanisminNSC34motor neuron-like cells.	Mice	……	[120]
Combined with evodiamine, increases 5-HTT RNA and protein expression in various alleles	Mice	……	[170]
Ameliorates b-amyloid pathology, gliosis, and cognitive impairment in an Alzheimer's disease	Transgenic Mice	……	[103]
Protective potential against the reserpine-induced nociceptive and depressive behavior	Mice	1 mg/kg SC	[171]
The hormetic and neuroprotective effects of berberine were confirmed to be mediated by up-regulated PI3K/AKT/Bcl-2 cell survival and Nrf2/HO-1 antioxidative signaling pathways. In addition, low dose berberine markedly mitigated the 6-OHDA-induced dopaminergic neuron loss and behavior movement deficiency in Zebrafish, while high dose.	Zebrafish neurotoxic models	……	[172]

with berberine and atorvastatin is more effective in preventing atherosclerotic processes than atorvastatin alone [190]. A new insight into the molecular mechanism of berberine and its therapeutic potential in the treatment of atherosclerosis was confirmed due to the fact that berberine inhibited inflammation by promoting autophagy through activation of the AMPK/mTOR signaling pathway [191]. Basic research findings suggested that the combination of berberine with verapamil could enhance brain uptake of berberine and provides a greater impact on neuroprotection in rat models of transient global cerebral ischemia [192]. It has been observed that berberine dramatically lessened neurological deficits scores *via* increasing the activation of PI3K/Akt signaling and claudin-5 and decreasing NF-κB expression in the ischemic brain [162, 193]. Berberine can decrease triglycerides, improve metabolic syndrome, have better glycemic control in diabetes and act directly on the vasculature to promote vascular health *via* its ability to activate adenosine monophosphate-activated kinase [194]. These compelling research findings demonstrate that berberine may inhibit the pathogenesis of atherosclerosis and has the potential to reduce a host of risk factors for AD.

CONCLUSION

Berberine has shown promising results in the management of symptomatic AD due to its ability to treat neurodegenerative disorders and anti-inflammatory activity. Berberine controls the production of β-amyloid, which is responsible for the AD-associated with tau and neurofibrillary tangle. There is a strong need to explore the studies on berberine at the molecular and cellular level to obtain more promising clinical significance in berberine based AD therapy.

LIST OF ABBREVIATIONS

AA	=	Anticholinergic Activity
Ach	=	Acetyl Cholinesterase's
AChE	=	Acetyl Cholinesterase's Enzyme
AD	=	Alzheimer's Disease
ADME	=	Absorption, Distribution, Metabolism, and Excretion
APOE	=	Apolipoprotein E
APP	=	Amyloid Precursor Protein
Aβ	=	Beta-Amyloid
BACE-1	=	Beta-Secretase 1
BBB	=	Blood–Brain Barrier
BPSD	=	Behavioral and Psychological Symptoms of Dementia
BuChE	=	Butylcholinesterase's Enzyme
CSF	=	Cerebro Spinal Fluid
CVD	=	Cardiovascular Disease
FDA	=	Food and Drug Administration
GSK-3β	=	Glycogen Synthase Kinase-3 Beta
HDAC	=	Histone Deacetylases
HDL	=	High Density Lipoprotein
JNK	=	Jun Amino-Terminal Kinases
LDL	=	Low Density Lipoprotein
NFT	=	Neurofibrillary Tangle
NSAIDs	=	Non-Steroidal Anti-Inflammatory Drugs.

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CONFLICT OF INTEREST

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

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