Berberine – A Neuropsychiatric Pharmacotherapy


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ABSTRACT
Increased longevity of life due to advanced healthcare facilities has led to an upsurge in the incidence of ailments like Alzheimer's disease. Various treatment modalities have been introduced to improve the quality of life of these patients. Therapies available for this condition include acetylcholinesterase inhibitors, N-methyl-D-aspartate receptor antagonists, antioxidants, lipid lowering agents and other newer modalities of pharmacotherapy which try to target the basic aetiopathogenesis of this disease. Berberine is one such promising treatment modality which has a plethora of pharmacological actions like reduction in amyloid β-42 production and formation of neurofibrillary tangles. It also inhibits acetylcholinesterase, reduces serum cholesterol and blood glucose. It has an anti-inflammatory, antioxidant property and improves glucagon like peptide-1 levels. Berberine has an additional antidepressant action which contributes to the overall well being of the patients of Alzheimer's disease. Thus berberine with its myriad of actions can be considered as a propitious treatment modality for Alzheimer's disease.

Keywords: berberine, alzheimer's disease, amyloid β-42, neurofibrillary tangles

INTRODUCTION
Alzheimer's disease is a progressive, degenerative disorder that attacks the neurons in the brain, resulting in loss of memory and also adversely affects thinking, language skills, and behaviour. Alzheimer's disease is the most common cause of dementia or loss of intellectual function among people aged 65 years and above, which does not constitute a normal part of ageing1. Alzheimer's disease (AD) is the fourth leading cause of death in developed nations ranking after cardiac disease, malignancy and stroke. AD affects about 2% of population at 65 years of age, with the incidence roughly doubling up every 5 years till the age of 90 years (≥50%). AD is much more prevalent in women than in men for any given age group2.

The world has witnessed a significant demographic evolution due to public health advances, as a consequence of which the proportion of the people above 60 years is growing faster than any age group leading to an alteration of the age pyramid. Hence it would be rational to assume that in this rapidly graying world, the incidence of non communicable diseases like AD will increase proportionately with the ageing population.

The aetiopathogenesis of AD is complex and mainly two mechanisms have been proposed, amyloid cascade hypothesis3 and two hit hypothesis4. The key event leading to AD has been postulated to be the formation of beta amyloid (Aβ) plaques which ultimately leads to the destruction of neurons. Aβ peptide specifically, amino acid peptide 42 (Aβ42) is hydrophobic and sticky and hence aggregates more readily, thus acting as a main culprit in causing cerebral vasoconstriction and impaired mitochondrial function. In contrast, Aβ 40 is water soluble and nonpathogenic. The Aβ peptides 40 and 42 are created by the enzymatic clipping of neuronal membrane bound protein called as amyloid precursor protein (APP) with the help of enzymes like secretases-alpha, beta and gamma. Beta secretase (BACE 1) and gamma secretase play an important role in the generation of Aβ 42 which clumps together to form insoluble amyloid plaques. These plaques damage the neurons due to inflammation and oxidative stress leading to the formation of neurofibrillary tangles (NFTs)5-7.

The ingredients required for neuronal function are synthesized in the neuronal cell body and are transported within the cell with the help of microtubules. Tau is an important protein that maintains the structural integrity of microtubules. In AD the tau proteins become hyperphosphorylated and lose their capacity to bind to the microtubules, instead they bind to each other, tying themselves in “knots” forming NFTs5. Neurons with NFTs rather than functional microtubules die sooner. Hence the formation of both tangles and plaques lead to AD. Fibrillar Aβ can induce mitogen activated protein kinase (MAPK) leading to tau phosphorylation and subsequently to the formation of NFTs although other kinases may be involved as well2.
The genetic inheritance of AD, as familial or sporadic form has been attributed to the chromosomes 41, 1, 21 and 19 which encode for genes like presenilin 1 and 2, amyloid precursor protein and apoprotein E (APOE)\(^1\). Apoproteins (APOs) are the protein portion of the lipoproteins (LDL, HDL, VLDL, etc) that transport cholesterol. Neurotoxicity due to A\(\beta\) is mediated, at least in part, by the lipid peroxidation product 4-hydroxynonenal (HNE). The cysteine residues of APOE3 and APOE2 protect against HNE neurotoxicity. But APOE4 has no cysteine residues and does not protect against covalent modification of proteins by HNE. Thus APOE4 allele is associated with higher plasma cholesterol levels and an even higher risk of AD\(^1\). A\(\beta\) binds to both copper and cholesterol, fostering the oxidation of cholesterol to the compounds that are extremely toxic to the neurons\(^12\).

The toxicity of A\(\beta\) 42 is often attributed to the aggregation of this peptide into a \(\beta\) sheet structure of ordered fibrils\(^13\). Acidic conditions in lysosomes and inflammation enhance A\(\beta\) aggregation. Cross-linking with advanced glycation end products (AGEs) stabilizes the amyloid plaques and accelerates the formation of \(\beta\) sheets. The receptor for advanced glycation end (RAGE) products may mediate the activation of microglia\(^14,15\). Microglia activated by A\(\beta\) produce inflammatory cytokines like interleukin1\(\beta\) (IL1\(\beta\)) and tumour necrosis factor alpha (TNF \(\alpha\)). A\(\beta\) also activates the transcription factor NF-\(\kappa\)B which increases cytokine production by neurons as well as by microglia\(^16\). Microglia induces enzymes such as nitric oxide synthase [NOS] which generate nitric oxide [NO] leading to peroxynitrite production and oxidative stress\(^17\). IL-1\(\beta\) further aggravates the immune/inflammatory response by promoting more APP synthesis and by enhancing the production of more A\(\beta\)-binding proteins by astrocytes\(^18\). Over-expression of IL-1 near amyloid plaques may promote the phosphorylation of tau protein, leading to the formation of NFTs and neuronal death\(^19\).

A\(\beta\) 42 causes oxidative stress and lipid peroxidation which induces neurotoxicity. This can be inhibited by antioxidants and vitamin E. A\(\beta\) 42 also inhibits creatinine kinase leading to decreased utilization of energy, altered assembly of cytoskeleton proteins and enhanced excitotoxicity to neurons by glutamate\(^20\). A\(\beta\)42 also enhances superoxide production by macrophages\(^21\).

There is evidence that aluminium is neurotoxic in both humans and experimental animals. Aluminium salts introduced in experimental animals could induce NFTs due to oxidative stress and apoptosis. It has an important role to play in the cell mediated excitotoxicity\(^22\). Neurons are normally non-dividing (post-mitotic) cells. But neurons that have entered in an aberrant cell cycle are frequently encountered in AD. Aberrant cell cycle induction may be the primary cause of neuronal death in AD and precede the formation of A\(\beta\) peptides as well as NFTs. Study of the hippocampal neurons in patients of both AD and mild cognitive impairment show that, 5-10% of neurons have cell cycle markers suggesting that cell cycle antigens could be of benefit in the early detection of AD\(^23\).

The "Two Hit Hypothesis" of AD suggests that chronic mild oxidative stress and extremely slow apoptotic rate, associated with aberrant cell cycles in neurons are both essential conditions for causation of AD. But neither of them alone is a sufficient cause. Formation of A\(\beta\) peptides and NFTs are secondary to the destructive processes leading to AD\(^24\).

The Neurotransmitter theory of AD states that, there is a marked decrease in choline acetyl transferase and loss of cholinergic neurons in the brain. Cholinergic neurons which originate from nucleus basalis in the forebrain and project to the frontal cortex and hippocampus and play a critical role in learning, memory and cognition are destroyed in AD. This has prompted the use of choline esterase inhibitors which can cross blood brain barrier. These drugs block the degradation of acetyl choline and increase its availability in the synaptic clefts\(^25\).

Other causes of AD have been postulated to be chronic smoking and atherosclerotic changes that affect the cerebral circulation, thereby inducing ischemia and oxidative stresses leading to AD. Similarly herpes simplex virus type 1 infection has also been reported to enhance the relative risk of developing AD\(^26\).

The current therapy for treatment of AD is categorized as –

- Treatment of primary symptoms- memory loss
- Treatment of secondary symptoms concerned with behavioural problems.

Therapies which address the memory loss in AD are—\(^27,28\)
Cholinesterase inhibitors e.g Donepezil, Rivastigmine, Galantamine and newer AChE inhibitors under trial like Huperzine and Lodostigil

N-methyl-D-asparate (NMDA) receptor antagonist- Mimentine

Newer therapeutic targets - a) Targets for decreasing A\(\beta\) peptide formation – \(\beta\) secretase and gamma secretase inhibitors b) Targets for preventing/ disrupting A\(\beta\) polymerization e.g Caprospinal, RAGE inhibitors etc. c) Targeting destruction of A\(\beta\) peptides with immunotherapy either by active or by passive immunization. d) Targeting prevention of tau mediated neurodegeneration e) Calcium channel blockers – Nilvadipine f) Targeting prevention of inflammatory cascade – perispinal injection of Itanercept g) Use of nerve growth factors h) Drugs targeting synaptic strengthening and efficient memory development – PDE 4 inhibitors

Antioxidants –e.g. Vit. E, Flavonoids, Curcumin, Selegiline, Melatonin, Co-enzyme Q10, Lipoic acid, Resveratrol, Pramipaxol, Ginko Biloba

Glucagon like peptide 1 (GLP 1) analogues – Liraglutide Lipid lowering agents - Statins

Despite the above mentioned promising modalities, treatment of AD still remains an enigma.

Diabetics are more prone for AD\(^29\). Berberine is being used successfully as an oral antidiabetic drug and the same has been found to benefit the patients of AD. This has provided an impetus for an extensive research
regarding berberine as a possible treatment modality for AD.

Berberine has multiple pharmacological effects. It can inhibit acetylcholinesterase, reduce blood cholesterol and blood glucose levels and has anti-inflammatory property. It can help to improve the survival, development and function of neurons and provide neuroprotection. Berberine can reduce the production of Aβ 42 plaques which have a pivotal role to play in neuronal degradation in AD. Berberine significantly decreases the production of Aβ 42. It also activates extra cellular signal regulated kinase ½ (ERK ½) which contributes to the reduction in the formation of NFT’s. Data indicate that berberine decreases the production of Aβ 42 by inhibiting the BACE expression via activation of ERK1/2 pathway. ERK ½ governs endogenous negative regulation of gamma secretase activity and hence inhibits the formation of plaques.

Different studies have postulated various mechanisms for the possible role of berberine in AD. Berberine suppresses Aβ induced inflammatory response in microglia by inhibiting NFκB by blocking MAPK signaling pathway. By inhibiting Aβ peptide, berberine decreases the production of IL6 and monocyte chemotactic protein 1. Berberine also downregulates the expression of cyclo-oxygenase 2 and NOS in microglia.

Simultaneous inhibition of phosphoinositide 3 kinase/pk b pathway is also observed. Tau– phosphorylation is significantly attenuated. As a result of this, production of IL-6, which is supposed to be stimulated by Aβ peptide gets markedly reduced. This in turn reduces neuroinflammation. Berberine also attenuates the glycogen synthase kinase 3 activity which is responsible for hyper phosphorylation of tau. Thus berberine prevents its phosphorylation. Berberine also activates ERK ½ pathways and decreases the expression of beta secretase resulting in reduced Aβ production.

Inhibitory effect on acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) – A striking deficiency of ACh due to atrophy & degeneration of subcortical cholinergic neurons particularly in basal forebrain that provides cholinergic innervation to cerebral cortex is seen in AD. AChE catalyses the acid hydrolyses of neurotransmitter ACh to choline in central and peripheral nervous systems which lead to transformation of activated cholinergic neuron to resting state. Hence number of studies have focused their attention on the effect of AChE inhibitors in the treatment of AD so that they can alleviate deficiency of ACh, resulting in improved neurotransmission. BChE also has an important role in the progression of AD. Genetic studies have found a link between a variant of BChE (BChE-k) and development of AD. This confirms the potential role of BChE inhibition in the treatment of AD. Studies have proved that berberine has an inhibitory effect on AChE. Xiang et al have explored the molecular mechanism underlying the inhibition of AChE by berberine. They proposed that an increase in favourable entropy enhances binding of berberine to AChE. This inhibition of AChE by berberine is an interaction as well as minor conformational change. In addition berberine also inhibits BChE. Thus berberine is a dual inhibitor of both AChE and BChE.

Monoamine oxidase (MAO) inhibitor activity – Berberine has been shown to have antidepressant effect in animal models. This action of berberine is mediated through change in brain dopamine, serotonin and norepinephrine levels. Modulation of NO pathway is also contributory for antidepressant effect. MAO-A and B are two isoforms of MAO. MAO-A inhibitors are proven antidepressants whereas MAO-B inhibition has a potential role to play in parkinsons and neurodegenerative diseases. Berberine has been demonstrated to inhibit both MAO-A and B. The mechanism underlying neuroprotective effect of MAO inhibitors in AD have been reviewed by Riederer et al.

Lipid lowering activity – Studies done by Wolozine et al have shown that lipid lowering drugs have decreased the incidence of AD. Simons et al have tried to find out relation of cholesterol with AD. Cholesterol might modulate the Aβ deposit formation. Decreased neuronal cholesterol can inhibit Aβ forming amyloidogenic pathway possibly by removing APP from the membrane microdomains. This reduces the role of Aβ in fibril formation.

Pugielli et al have proposed the molecular mechanism underlying the cause effect relationship of cholesterol with AD. Cholesterol lowering drugs have good potential to combat AD. It was proved that berberine effectively reduces total serum cholesterol and LDL cholesterol in the hyperlipidemic patients. But the mechanism of cholesterol lowering action of berberine differs from that of statins.

Antioxidant activity – It is well known that oxidative damage plays a vital role in the pathogenesis of AD. Cellular oxidative stress and /or nitrosative stress including augmentation of protein oxidation, protein nitration, glycol oxidation and lipid peroxidation governs the pathogenesis of AD. Antioxidant property of berberine is already well documented. Berberine can scavenge reactive oxygen species (ROS) and reactive nitrogen species (RNS). Among RNS peroxinitrites (ONOO⁻) are generated as a result of reaction between NO and superoxide. Anion radical has been implicated in the formation and accumulation of Aβ. Berberine scavenges both NO and ONOO⁻. Berberine also has protective effect against low density lipoprotein oxidation and also inhibits lipid peroxidation.

Other mechanisms which contribute for action of berberine in AD. Diabetics have higher incidence of AD which is attributed to the impairment of insulin signaling in the brain. GLP-1 analogue iraglutide was tried in mouse model of AD and has proved to have preventive role in neurodegeneration.

Safety and efficiency of berberine is proved in the treatment of DM type 2. It also has anti AD potential. Rat model of streptozocin induced diabetes was used to confirm the beneficial effect of berberine in ameliorating memory dysfunction. GLP-1 has been
proved to be neuroprotective and is a proposed new therapeutic agent in AD. Berberine is known to increase GLP-1. This effect of berberine on GLP-1 contributes to the treatment of AD. Mitochondrial dysfunction and energy deficiency are the early features of AD. Mitochondria play a central role in mediating neuronal stress which can contribute to the pathogenesis of AD. The mitochondrial effects of berberine are well documented. Berberine protects the neurons against neurotoxicity. An excessive release of glutamate is one of the molecular mechanisms of neuronal damage in several neurological disorders. In the study done by Lin T et al inhibitory effect of berberine on glutamate release was observed. It was associated with reduction in depolarization induced increase in cytosolic free calcium concentration. Involvement of ca.2.1 (P/Q-type) channel was confirmed. 

Berberine and depression
Animal studies done using berberine injection revealed its antidepressant effect. Reserpine is known to induce depression by depleting brain catecholamines. Berberine is proved to be effective in reversing reserpine induced depression. It has also enhanced the action of other commonly used antidepressants like imipramine, fluoxetine and venlafaxine.

Sigma receptors are the new targets for antidepressant pharmacotherapy. These are intracellular receptors expressed on endoplasmic reticulum. Their activation may modulate glutameric signaling such as NMDA. They regulate calcium signaling in endoplasmic reticulum and cytoplasm.

Sigma receptors 1 enhance antidepressant effects. Berberine is a known positive modulator of sigma receptors and hence considered as a new class of drug for treatment of depression. It has shown its antidepressant effects mediated by altering brain dopamine, serotonin and norepinephrine levels in animal models. Modulation of NO pathway also contributes for its antidepressant effect. Berberine is known to inhibit enzyme MAO which reflects as increased catecholamines in the brain contributing to its antidepressant effect. Berberine enhances neural serotonin and raises dopamine level too.

Sedation - Berberine has shown to have sedative property in higher doses in animal models.

Analgesia – Berberine given for long term in animal models has reduced the pain induced by tail-flich test. Addiction and dependence – Berberine when studied in rats, was known to reduce morphine induced withdrawal behavior possibly through the modulation of hypothalamic corticotrophin releasing factor (CRF) and the central noradrenergic system. Hence berberine may be a useful agent to treat or to reduce withdrawal symptoms.

Thus berberine has multiple neuropharmacological properties which encompass reduced neuronal apoptosis, improved cerebral micro circulation which contribute to its therapeutic use in AD. Berberine is not easily absorbed from human and animal GI tract, which affects its bioavailability. Hence studies of its pharmacokinetic properties are warranted as it can be a potential tool to treat neurological disorders. A study done with berberine suggested that it induces senescence of human glioblastoma cells by down regulating EGFR-MEK-ERK signaling pathway. This demands extensive studies regarding its movement across blood brain barrier and concentration in CSF to confirm its CNS bioavailability.

CONCLUSION
Berberine possesses multiple pharmacological effects which contribute to its potential role in the treatment of AD. Its actions like inhibition of acetylcholinesterase and butyrylcholinesterase, antioxidant and anti-inflammatory activity, inhibition of MAO along with reduction of Aβ levels in the CNS and lowering of cholesterol help in amelioration of AD. Safety of berberine is well documented. Berberine used in clinical doses is proved to be non toxic and is devoid of genotoxic, cytotoxic or mutagenic activity. It can be conveniently administered orally. It is known to cross blood brain barrier. Hence it can be summarized that due to its pluripotent action, berberine can be considered as a promising therapeutic tool in the treatment of AD.

CONFLICTS OF INTEREST – none declared

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