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Review Article

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-asparate 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, alzheimers 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 ageing[1].

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 group[2].

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 hypothesis[3] and two hit hypothesis[4]. 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 (Aß42) 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 NFTs[8]. Neurons with NFTs rather than functional microtubules die sooner. Hence the formation of both tangles and plaques lead to AD. Fibrillar Aß 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 well[9].

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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)[10].

Apoproteins (APOs) are the protein portion of the lipoproteins (LDL, HDL, VLDL, etc) that transport cholesterol. Neurotoxicity due to Aß 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[11]. Aß 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 Aβ 42 is often attributed to the aggregation of this peptide into a β sheet structure of ordered fibrils[13]. Acidic conditions in lysosomes and inflammation enhance Aβ aggregation. Cross-linking with advanced glycation end products (AGEs) stabilizes the amyloid plaques and accelerates the formation of ß sheets. The receptor for advanced glycation end (RAGE) products may mediate the activation of microglia.[14,15]. Microglia activated by Aβ produce inflammatory cytokines like interleukin1β (IL1β) and tumour necrosis factor alpha (TNF α). Aβ also activates the transcription factor NF−κB 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-1ß further aggravates the immune/inflammatory response by promoting more APP synthesis and by enhancing the production of more Aß-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].

Aβ 42 causes oxidative stress and lipid peroxidation which induces neurotoxicity. This can be inhibited by antioxidants and vitamin E. Aβ 42 also inhibits creatinine kinase leading to decreased utilization of energy, altered assembly of cytoskeleton proteins and enhanced excitotoxicity to neurons by glutamate[20]. Aß42 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 Aß 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 Aβ 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 Donepazil, 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 Aβ peptide formation – β secretase and gamma secretase inhibitors b) Targets for preventing/ disrupting Aβ polymerization e.g Caprospinol, RAGE inhibitors etc. c) Targeting destruction of Aβ 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[30].

Berberine has multiple pharmacological effects. It can inhibit acetylcholinesterase, reduce blood cholesterol and blood glucose levels and has anti-inflammatory property[30-33]. It can help to improve the survival, development and function of neurons and provide neuroprotection[34]. Berberine can reduce the production of Aβ 42 plaques which have a pivotal role to play in neuronal degradation in AD[35]. 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[7]. 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[36].

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[37].

Simultaneous inhibition of phosphoinositide 3 kinase/pk b pathway is also observed[38] 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[39]. Berberine also activates ERK ½ pathways and decreases the expression of beta secretase resulting in reduced Aβ production [34,40].

Inhibitory effect on acetylcholinesterase (AChE) and butylcholinesterase (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[41,42]. 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[43]. This confirms the potential role of BChE inhibition in the treatment of AD. Studies have proved that berberine has an inhibitory effect on AChE[44-46]. Xiang et al have explored the molecular mechanism underlying the inhibition of AChE by berberine[47]. 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[47].

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[48]. 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[49 -52]. The mechanism underlying neuropotective effect of MAO inhibitors in AD have been reviewed by Riederer et al.[53].

Lipid lowering activity – Studies done by Wolozine et al have shown that lipid lowering drugs have decreased the incidence of AD[54]. 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[55].

Puglielli 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[56]. 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[57].

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[58-61]. Antioxidant property of berberine is already well documented. Berberine can scavenge reactive oxygen species (ROS) and reactive nitrogen species (RNS). Among RNS perioxinitrites ($ONOO^-$) 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 $ONOO^-$[62]. Berberine also has protective effect against low density lipoprotein oxidation and also inhibits lipid peroxidation[62,63].

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[64]. GLP-1 analogue liraglutide was tried in mouse model of AD and has proved to have preventive role in neurodegeneration[65].

Safety and efficiency of berberine is proved in the treatment of DM type 2. It also has anti AD potential.[66,67] Rat model of streptozocin induced diabetes was used to confirm the beneficial effect of berberine in ameliorating memory dysfunction[68]. 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[69, 70].

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[71].The mitochondrial effects of berberine are well documented. Berberine protects the neurons against neurotoxicity. An excessive release of glutamate is one of the molecular mechanism 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 $ca_v2.1$ (P/Q-type) channel was confirmed[72].

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[48].

Sigma receptors are the new targets for antidepressant pharmacotherapy. These are intracellular receptors expressed on endoplasmic reticulum[73]. Their activation may modulate glutaminergic signaling such as NMDA[74]. They regulate calcium signaling in endoplasmic reticulum and cytoplasm[75].

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[48,77]. It has shown its antidepressant effects mediated by altering brain dopamine, serotonin and norepinephrine levels in animal models[48]. Modulation of NO pathway also contributes for its antidepressant effect[48,76]. Berberine is known to inhibit enzyme MAO which reflects as increased catecholamines in the brain contributing to its antidepressant effect[76]. Berberine enhances neural serotonin and raises dopamine level too[48, 76].

Sedation - Berberine has shown to have sedative property in higher doses in animal models[48].

Analgesia – Berberine given for long term in animal models has reduced the pain induced by tail- flich test[48].

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[77].

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[78].

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[79].

CONCLUSION

Berberine possesses multiple pharmacological effects which contribute to its potential role in the treatment of AD. Its actions like inhibition of acetylycholinesterase and butylcholinesterase, 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

REFERENCES

1. http://www.alzfdn.org/AboutAlzheimers/definition.html accessed on 21/1/15
2. http://www.who.int/medicines/areas/priority_medicines/BP6_11Alzheimer.pdf accessed on 21/1/15
3. Karran E, Mercken M, Strooper *BD.* The amyloid cascade hypothesis for Alzheimer's disease: an appraisal for the development of therapeutics. *Nature reviews* 2011, 10, 698 -712.
4. Zhu X, Lee HG, Perry G, Smith MA. Alzheimer disease, the two-hit hypothesis: an update. Biochim Biophys Acta. 2007 Apr;1772(4):494-502.
5. Stefani M and Rigacci S. Protein Folding and Aggregation into Amyloid: The Interference by Natural Phenolic Compounds. *Int J Mol Sci*, 2013, 14, 12411–12457.
6. Gella A and Durany N. Oxidative stress in Alzheimer disease. Cell Adh Migr, 2009, 3, 88–93.
7. Panahi N, Mahmoudian M, Mortazavi P, Hashjin GS. Effects of berberine on β-secretase activity in a rabbit model of Alzheimer's disease. Arch Med Sci, 2013, 9, 146-50.
8. Chew Y, Fan X, Götz J, Nicholas H. Regulation of age-related structural integrity in neurons by protein with tau-like repeats (PTL-1) is cell autonomous. Journal name: Scientific Reports 2014, Volume:4, 1-9.
9. Rapoport M and Ferreira A. PD98059 Prevents Neurite Degeneration Induced by Fibrillar b-Amyloid in Mature Hippocampal Neurons. J. Neurochem, 2000, 74, 125–133.
10. Bekris L, Chang-En Yu, Bird T, Tsuang D. Genetics of Alzheimer Disease. J Geriatr Psychiatry Neurol, 2010, 23, 213–227.

11. Pedersen WA, Chan SL, Mattson MP. A mechanism for the neuroprotective effect of apolipoprotein E: isoform-specific modification by the lipid peroxidation product 4-hydroxynonenal. J Neurochem. 2000;74(4):1426-1433.
12. Nelson TJ and Alkon DL. Oxidation of cholesterol by amyloid precursor protein and beta amyloid peptide. *J biol chem,* 2005, 280, 7377-7387.
13. Iversen L, Mortishire-Smith R, Pollack S, Shearman M. The toxicity in vitro of β-amyloid protein. *Biochem. J*, 1995, 311, 1-16.
14. Iannuzzi C, Irace G, Sirangelo I. Differential effects of glycation on protein aggregation and amyloid formation. Front. Mol. Biosci, 2014, 1, 1-8.
15. Yan S, Chen X, Fu J, Chen M, Zhu H, Roher A, Slattery T, Zhao L, Nagashima M, Morser J, Migheli A, Nawroth P, Stern D, Schmidt A. RAGE and amyloid- peptide neurotoxicity in Alzheimer's disease. *Nature, 1996*, 382, 685-691.
16. Mark P and Camandola S. NF-κB in neuronal plasticity and neurodegenerative disorders. *Journal of Clinical Investigation*, 2001, 107, 247-254.
17. Jianrong L, Baud O, Vartanian T, Volpe J, Rosenberg P. Peroxynitrite generated by inducible nitric oxide synthase and NADPH oxidase mediates microglial toxicity to oligodendrocytes. Proceedings of the National Academy of Sciences of the United States of America, 2005, 102, 9936-9941.
18. Meda L, Baron P, Scarlato G. Glial activation in Alzheimer's disease: the role of Aβ and its associated proteins. *Neurobiology of ageing*, 2001, 22, 885–893.
19. Sheng J, Jones R, Zhou X, McGinness J, Eldik L, Mrak R, Griffin W. Interleukin-1 promotion of MAPK-p38 overexpression in experimental animals and in Alzheimer's disease: potential significance for tau protein phosphorylation. *Neurochemistry International*, 2001, 39, 341-348.
20. Butterfield D, Castegna A, Lauderback C, Drake J. Evidence that amyloid beta-peptide-induced lipid peroxidation and its sequelae in Alzheimer's disease brain contribute to neuronal death. *Neurobiol Aging*, 2002, 23,655-64.
21. Calhoun WJ, Reed HE, Moest DR, Stevens CA. Enhanced superoxide production by alveolar macrophages and air-space cells, airway inflammation, and alveolar macrophage density changes after segmental antigen bronchoprovocation in allergic subjects. *Am Rev Respir Dis*, 1992, 145,317-25.
22. Bharathi P, Vasudevaraju M, Palanisamy A, Sambamurti K, Rao KSJ. Molecular toxicity of aluminium in relation to neurodegeneration *Indian J Med Res, 2008,* 128, 545-556.
23. Yang Y, Mufson E, Herrup K. Neuronal Cell Death Is Preceded by Cell Cycle Events at All Stages of Alzheimer's Disease. *The Journal of Neuroscience*, 2003, 23, 2557–2563.
24. Zhu X, Raina AK, Perry G, Smith MA. Alzheimer's disease: the two-hit hypothesis. Lancet Neurol. 2004 ; 3(4):219-26.
25. Sabbagh MN, Lukas RJ, Sparks DL, Reid RT. The nicotinic acetylcholine receptor, smoking, and Alzheimer's disease. *J Alzheimers Dis*, 2002, 4, 317-25.
26. Lin WR, Casas I, Wilcock GK, Itzhaki RF. Neurotropic viruses and Alzheimer's disease: a search for varicella zoster virus DNA by the polymerase chain reaction. *J Neurol Neurosurg Psychiatry*, 1997, 62, 586-589.
27. Aprahamian I, Stella F, Forlenza O. New treatment strategies for Alzheimer's disease: is there a hope? *Indian J Med Res*, 2013, 138, 449–460.
28. Singh S, Kushwah AS, Singh R, Farswan M, Kaur R. Current therapeutic strategy in Alzheimer's disease. *Eur Rev Med Pharmacol Sci*, 2012,16,1651-64.
29. Pasquier F, Boulogne A, Leys D, Fontaine P. Diabetes mellitus and dementia. *Diabetes Metab*, 2006, 32, 403–414.
30. Cicero AF and Tartagni E. Antidiabetic properties of berberine: from cellular pharmacology to clinical effects. *Hosp Pract* 1995, 2012, 40, 56-63.
31. Huang L, Shi A, He F, Li X. Synthesis, biological evaluation, and molecular modeling of berberine derivatives as potent acetylcholinesterase inhibitors. *Bioorganic & Medicinal Chemistry*, 2010, 18, 1244–1251.
32. Doggrell SA. Berberine-a novel approach to cholesterol lowering. *Expert Opin Investig Drugs*, 2005, 14, 683-685.
33. Li Z, Geng Y, Jiang J, Kong W. Antioxidant and Anti-Inflammatory Activities of Berberine in the Treatment of Diabetes Mellitus. *Evidence-Based Complementary and Alternative Medicine*, 2014, 14, 1-12.
34. Zhang X, Zhang X, Wang C, Li Y, Dong L, Cui L, Wang L, Liu Z, Qiao H, Zhu C, Xing Y, Cao X, Ji Y, Zhao K. Neuroprotection of early and short-time applying berberine in the acute phase of cerebral ischemia: up-regulated pAkt, pGSK and pCREB, down-regulated NF-κB expression, ameliorated BBB permeability. *Brain Res*, 2012, 12, 61-70.
35. Zhu F, Wu F, Ma Y, Liu G, Li Z, Sun Y, Pei Z. Decrease in the production of beta-amyloid by berberine inhibition of the expression of beta-secretase in HEK293 cells. *BMC neuroscience*, 2011, 12,1-8.
36. Zhu F, Wu F, Ma Y, Liu G, Li Z, Sun Y, Pei Z. Decrease in the production of β-amyloid by berberine inhibition of the expression of β-secretase in HEK293 cells. BMC Neurosci. 2011 Dec 12;12:125.
37. Jia L, Liu J, Song Z, Pan X, Chen L, Cui X, Wang M. Berberine suppresses amyloid-beta-induced inflammatory response in microglia by inhibiting nuclear factor-kappaB and mitogen-activated protein kinase signalling pathways. *J Pharm Pharmacol*, 2012, 64, 1510-21.
38. Jackson D and Setzer W. Selective phosphoinositide 3-kinase inhibition by natural products:A molecular docking study. *Der Pharma Chemica*, 2013, 5, 303-311.

39. Durairajan SS, Liu LF, JH Lu, Chen LL, Yuan Q, Chung SK, Huang L, Li XS, Huang JD, Li M. Berberine ameliorates beta-amyloid pathology, gliosis, and cognitive impairment in an Alzheimer's disease transgenic mouse model. *Neurobiology of Aging*, 2012, 33, 2903–2919.
40. Asai M, Iwata N, Aizaki A, Ishiura S, Saido TC, Maruyama K. Berberine alters the processing of Alzheimer's amyloid precursor protein to decrease Aβ secretion. *Biochemical and Biophysical Research Communications*, 2007, 352, 498–502.
41. Muñoz-Torrero D. Acetylcholinesterase inhibitors as disease-modifying therapies for Alzheimer's disease. *Curr. Med. Chem*, 2008, 15, 2433-2455.
42. Scarpini E, Scheltens P, Feldman H. Treatment of Alzheimer's disease: Current status and new perspectives. *Lancet Neuro*, 2003, 2, 539-547.
43. Lehmann D, Johnston C, Smith AD. Synergy between the genes for butyrylcholinesterase K variant apolipoprotein E4 in late-onset confirmed Alzheimer's disease. *Hum. Mol. Genet*, 1997, 6,933-935.
44. Huang L, Shi A, He F, Li X. Synthesis, biological evaluation, and molecular modeling of berberine derivatives as potent acetylcholinesterase inhibitors. *Bioorg. Med. Chem*, 2010, 18, 1244-1251.
45. Kim DK, Lee KT, Baek NI, Kim SH, Park HW, Lim JP, Shin TY, Eom D, Yang JH, Eun JS. Acetylcholinesterase inhibitors from the aerial parts of Corydalis speciosa. *Arch. Pharm. Res.* 2004, 27, 1127-1131.
46. Huang L, Luo Z, He F, Shi A, Qin F, Li X. Berberine derivatives, with substituted amino groups linked at the 9-position, as inhibitors of acetylcholinesterase/butyrylcholinesterase. *Bioorg.Med. Chem. Lett*. 2010, 20, 6649-6652.
47. Xiang J, Yu C, Yang F. Conformation-activity studies on the interaction of berberine with acetylcholinesterase: Physical chemistry approach. *Prog. Nat. Sci.* 2009, 19, 1721-1725.
48. Kulkarni SK and Dhir A. On the mechanism of antidepressant-like action of berberine chloride. *European Journal of Pharmacology*, 2008, 589, 163–172.
49. Riederer P, Lachenmayer L, Laux G. Clinical applications of MAO-inhibitors. *Curr. Med. Chem.* 2004, 11, 2033-2043.
50. Kong LD, Cheng CH, Tan RX. Monoamine oxidase inhibitors from rhizoma of Coptis chinensis. *Planta Med*. 2001, 67, 74-76.
51. Lee SS, Kai M, Lee MK. Effects of natural isoquinoline alkaloids on monoamine oxidase activity in mouse brain: Inhibition by berberine and palmatine. *Med. Sci. Res*. 1999, 27, 749-751.
52. Castillo J, Hung J, Rodriguez M, Bastidas E, Laboren I, Jaimes A. LED fluorescence spectroscopy for direct determination of monoamine oxidase B inactivation. *Anal. Biochem*. 2005, 343, 293-298
53. Riederer P, Danielczyk W, Grünblatt E. Monoamine oxidase-B inhibition in Alzheimer's disease. *Neurotoxicology*, 2004, 25, 271-277.
54. Wolozin B, Kellman W, Ruosseau P, Celesia GG, Siegel G. Decreased prevalence of Alzheimer disease associated with 3-hydroxy-3-methyglutaryl coenzyme A reductase inhibitors. *Arch. Neurol.* 2000, 57, 1439-1443.
55. Simons M, Keller P, Dichgans J, Schulz JB. Cholesterol and Alzheimer's disease: Is there a link? *Neurology*, 2001, 57, 1089-1093.
56. Puglielli L, Tanzi RE, Kovacs DM. Alzheimer's disease: The cholesterol connection. *Nat. Neurosci*. 2003, 6, 345-351.
57. Kong W, Wei J, Abidi P, Lin M, Inaba S, Li C, Wang Y, Wang Z, Si S, Pan H. Berberine is a novel cholesterol-lowering drug working through a unique mechanism distinct from statins. *Nat. Med*. 2004, 10, 1344-1351.
58. Jomova K, Vondrakova D, Lawson M, Valko M. Metals, oxidative stress and neurodegenerative disorders. *Mol. Cell Biochem*, 2010, 345, 91-104.
59. Markesbery WR. Oxidative stress hypothesis in Alzheimer's disease. *Free Radic. Biol. Med*, 1997, 23, 134-147.
60. Agostinho P, Cunha RA, Oliveira C. Neuroinflammation, oxidative stress and the pathogenesis of Alzheimer's disease. *Curr. Pharm. Des*, 2010, 16, 2766-2778.
61. Butterfield DA, Reed T, Newman SF, Sultana R. Roles of amyloid beta-peptide-associated oxidative stress and brain protein modifications in the pathogenesis of Alzheimer's disease and mild cognitive impairment. *Free Radic. Biol. Med.* 2007, 43, 658-677.
62. Yokozawa T, Ishida A, Kashiwada Y, Cho EJ, Kim HY, Ikeshiro Y. Coptidis Rhizoma: protective effects against peroxynitrite-induced oxidative damage and elucidation of its active components. J Pharm Pharmacol. 2004;56(4):547-56.
63. Hsieh YS, Kuo WH, Lin TW, Chang HR, Lin TH, Chen PN, Chu SC. Protective effects of berberine against low-density lipoprotein (LDL) oxidation and oxidized LDL-induced cytotoxicity on endothelial cells. *J. Agric. Food Chem*. 2007, 55, 10437-10445.
64. Akter K, Lanza EA, Martin SA, Myronyuk N, Rua M, Raffa RB. Diabetes mellitus and Alzheimer's disease: Shared pathology and treatment? *Br. J. Clin. Pharmacol*. 2011, 71, 365-376.
65. McClean PL, Parthsarathy V, Faivre E, Hölscher C. The diabetes drug liraglutide prevents degenerative processes in a mouse model of Alzheimer's disease. *J. Neurosci*. 2011, 31, 6587-6594.
66. Zhang Y, Li X, Zou D, Liu W, Yang J, Zhu N, Huo L, Wang M, Hong J, Wu P. Treatment of type 2 diabetes and dyslipidemia with the natural plant alkaloid berberine. *J. Clin.Endocrinol. Metab.* 2008, 93, 2559-2565.
67. Yin J, Xing H, Ye J. Efficacy of berberine in patients with type 2 diabetes mellitus. *Metabolism*, 2008, 57, 712-717.
68. Bhutada P, Mundhada Y, Bansod K, Tawari S, Patil S, Dixit P, Umathe S, Mundhada D. Protection of

cholinergic and antioxidant system contributes to the effect of berberine ameliorating memory dysfunction in rat model of streptozotocin-induced diabetes. *Behav. Brain Res*. 2011,220, 30-41.
69. Yu Y, Liu L, Wang X, Liu X, Liu X, Xie L, Wang G. Modulation of glucagon-like peptide-1 release by berberine: In vivo and in vitro studies. *Biochem. Pharmacol*. 2010, 79, 1000-1006.
70. Hölscher C. The role of GLP-1 in neuronal activity and neurodegeneration. *Vitam. Horm*. 2010,84, 331-354
71. Chen JX, Yan SS. Role of mitochondrial amyloid-beta in Alzheimer's disease. *J. Alzheimer's Dis*. 2010, 20, 569-S578.
72. Lin T, Lin Y, Lu C, Huang S, Wang S. Berberine Inhibits the Release of Glutamate in Nerve Terminals from Rat Cerebral Cortex. PLOS ONE 2013, 8, e67215.
73. Su TP and Hayashi T. Understanding the molecular mechanism of sigma-1 receptors: towards a hypothesis that sigma-1 receptors are intracellular amplifiers for signal transduction. *Curr Med Chem*. 2003, 10, 2073-80.
74. Debonnel G. Current hypotheses on sigma receptors and their physiological role: possible implications in psychiatry. *J Psychiatry Neurosci.* 1993, 18, 157–172.
75. Monnet FP. Sigma-1 receptor as regulator of neuronal intracellular Ca2+: clinical and therapeutic relevance. *Biol Cell*. 2005, 97, 873-83.
76. Kulkarni SK and Dhir A. Possible involvement of L-arginine-nitric oxide (NO)-cyclic guanosine monophosphate (cGMP) signaling pathway in the antidepressant activity of berberine chloride. *Eur J Pharmacol*. 2007, 13, 77-83.
77. Lee B, Sur B, Yeom M, Shim I, Lee H, Hahm D. Effect of Berberine on Depression- and Anxiety-Like Behaviors and Activation of the Noradrenergic System Induced by Development of Morphine Dependence in Rats. *Korean J Physiol Pharmacol*. 2012, 16, 379–386.
78. Ye M, Fu S, Pi R, He F. Neuropharmacological and pharmacokinetic properties of berberine: a review of recent research. J Pharm Pharmacol. 2009 Jul;61(7):831-7. doi: 10.1211/jpp/61.07.0001.
79. Liu Q, Xu X, Zhao M, Wei Z, Li X, Zhang X, Liu Z, Gong Y, Shao C. Berberine induces senescence of human glioblastoma cells by downregulating the EGFR-MEK-ERK signaling pathway. Mol Cancer Ther. 2015 Feb;14(2):355-63.