



PLANT BASED INDIAN TRADITIONAL MEDICINE FOR NEURODEGENERATIVE DISEASES - A NOVEL APPROACH TO TREAT ALZHEIMER

PRASEETHA P K^{1*}, PRATHEEBA¹, LATHIKA SOMASUNDARAM² AND G. SAKTHIVEL¹

¹Department of Nanotechnology, Noorul Islam Centre for Higher Education, Kumaracoil, Thuckalay, Tamilnadu, India - 629180.

²Inbiotics, William Hospital Campus, Nagercoil, Kanyakumari District, Tamilnadu, India - 629001.

ABSTRACT

As per the earlier reports, the most prevalent disease of Alzheimer's, a kind of dementia, affects approximately 24 million people worldwide. There may be many invisible reasons for the disease to be caused and the common evidences for the disease is due to a few reasons like aggregation of self-assembled fibrous proteins and variation in the level of Acetyl choline (ACh). Traditional Indian herbs which are rich in natural alkaloids and are an important source of acetyl-cholinesterase (AChE) which can restore the levels of acetylcholine. Bioactive compounds like Coumarins, flavonoids and other indirect sources from herbs can activate the complexes of the deadly disease, so that the derivatives work against the severity of the disease. The natural compounds derived from herbs can act as modulators and inhibitors for amyloid accumulation so that they can also suppress inflammation and neuronal cytotoxicity. These bioactive compounds have the advantage of being multi-targeted and hence are advantageous over the single target drugs in the treatment of such complex diseases. This review suggests the possibilities of using traditional Indian herbs which are a rich source of these compounds to effectively treat Alzheimer's disease and hence has attracted attention towards research and development of the therapies.

KEYWORDS: Alzheimer's, phyto-active agents, neurodegenerative diseases, plant extracts, antioxidants



PRASEETHA P K

Department of Nanotechnology, Noorul Islam Centre for Higher Education, Kumaracoil, Thuckalay, Tamilnadu, India - 629180.

INTRODUCTION

Neurodegenerative diseases primarily affects the brain and leads to cognitive impairment combined with motor deficits mostly reported in the aged populations. Alzheimer diseases and Parkinson disease are the most prominent aging related neurodegenerative diseases. Among these Alzheimer disease is a common neurodegenerative disorder reported in many victims leading to dysfunction, memory loss, language deficits, depression and behavioral problems¹⁻². Several Indian medicinal plants have been used in the Indian traditional Ayurveda system called rasayana which has been one of the most extensive traditional systems to treat neurodegenerative diseases³. The early process of the Indian traditional system of medicine deals with the phenomena of endogenous or exogenous processes which cause physiological disequilibrium leading to the pathological state. Three different plant species have been analyzed for their neuroprotective effect to cure Alzheimers disease⁴. The development of traditional based medicine mainly focused on three approaches such as isolated single compound, poly-herbal mixture and pharmacological and therapeutic effects of herbal extracts on specific diseases. In this review we discuss the development of each approach along with the advantage and dis-advantage.

ISOLATION OF BIOACTIVE COMPOUNDS

Several parts of the herbal plants such as roots, leaves, stems, barks, flowers and fruits are commonly rich in phenolic and other secondary metabolite compounds⁵. The pharmacological property of each compound differed in their active principles and many Indian medicinal plant composites are represented as neuroprotective and neuro-pharmacologically active compounds. Reports suggest that the anti-inflammatory and anti-oxidant properties of the medicinal plants are optimal for neurodegenerative diseases like Alzheimer. Oxidative stress induced by ROS free radicals have been suggested to play a major role in ageing and neurodegenerative diseases by means of increase dopamine oxidation in nigral dopaminergic neurons⁶. The proteolytic cleavage of the transmembrane amyloid precursor proteins leads to the formation of Amyloid β -peptide which induced extensive oxidative stress in neurons by means of lipid peroxidation and protein oxidation⁷. More over, the extracellular deposits of Amyloid β -peptide and PrP amyloid fibrils induce non-immune mediated chronic inflammatory responses and over deposition of high level of fibrillary amyloid β -peptide which is associated with loss of synapses and impairment of neuronal function leading to the risk factor for Alzheimer⁸⁻¹⁰. These reports suggest the possibility of the antioxidant compounds from the herbal plant can reduce the risk of Alzheimer by suppressing the oxidative stress. The use of isolated compound calebin-A, curcumin, dimethoxy curcumin, bis-demethoxy curcumin from *Curcuma longa* L., Zingiberaceae has been described effectively against Alzheimer by means of protection from β A(1-42) through antioxidant pathway¹¹. Nongnut *et al.*, described the saponins and

glycosides isolated from perennial creeping plant *Bacopama nniera* Linn. which exhibited lipid peroxidation inhibitory activity and neuroprotection against Alzheimer disease¹². A flavonoid kaempferol isolated from *Ginkgo biloba* leaves were potentially neuro-protectant as described elsewhere¹³. The inhibition of noise stress induced changes in the rat brain was determined by a novel drug α -asarone from *Acorus calamus*¹⁴. Glabridin isolated from *Glyocyrrhiza glabra* (*liquorice*) showed neuroprotective effect on pathways associated with an apoptosis¹⁵. Reports are available on arabinogalactan polysaccharide isolated from *Tinospora cordifolia* (*Menispermaceae*) which revealed protection against iron-mediated lipid peroxidation in rat brain cellular glutathione¹⁶. The neuroprotective compound FrB from *Convolvulus Pluricaulis choi*. (*Convolvulaceae*) stimulates the antioxidant mechanism in brain has been reported¹⁷. 4-hydroxyisophthalic acid an antioxidant compound isolated from *Decalepis hamiltonii* roots are reported as neuroprotective agent¹⁸⁻¹⁹. An acetylcholinesterase (AChE) inhibitor compound catechol alkenyls from *Semecarpus anacardium* L. f. (*Anacardiaceae*) was reported in earlier studies²⁰. The saponin rich fraction of *Ficus religiosa* L. (*Moraceae*) showed anticonvulsant activity against epileptic seizures induced synchronous neuronal activity in the brain has been reported earlier²¹. The anti-depressant activity in mouse brain monoamine neurotransmitters by means of reduced monoamine oxidase (MAO)-A level has been demonstrated²². Another compound iso-curcumenol from *Cyperus rotundus* L. (*Cyperaceae*) acts as a benzodiazepine receptor against an allosterically modulated GABAergic neurotransmission²³. The asiatican triterpenoid and madecassic acid from *Centella asiatica urban* (*Umbelliferae*) were reported as neuro protective agent²⁴⁻²⁶. The anti-epileptogenic activity of thymol isolated compound from *Carum copticum Benth* (*Apiaceae*) by means of neuronal Na⁺ channel blocking, positive allosteric modulation of GABA_A receptor and also due to its antioxidant properties was studied²⁷. The neuro protective agent embelin isolated from *Embelia ribes* *Burm.* (*Myrsinaceae*) was reported as a good remedy to treat brain damage, stroke and depression. Another report suggests embelin can inhibit glioma by blocking NF- κ B activity²⁸⁻³⁰. A patent compound vicenin-2 was reported for its potential neurological activity to control Alzheimer³¹. It was stated that the acetylcholinesterase (AChE) inhibiting nature of coumarin isolated from *Lantana camara* (*Verbenaceae*)³². The polyphenol xanthone compound mangiferin isolated from *Mangifera indica* L. (*Anacardiaceae*) claims to be a potential agent in the treatment of Alzheimer's disease. Moreover another report suggests that mangiferin interacts with the central neural components as secondarily peripheral target specifically instead of direct interaction with the neural components³³. With the available background information, it has been suggested that the anti-depressant activity of *Hypericum perforatum* L. purified compound hyperforin will enhance the concentration of monoamines and glutamate in the synaptic cleft³⁴⁻³⁵. The neuroprotective effect of polysaccharides purified from *Momordica charantia* (*Cucurbitaceae*) which inhibits c-Jun N-terminal protein kinase (JNK3) signaling

pathway inducing intracerebral hemorrhage injury has been described³⁶. Another recent experimental study suggests that *Momordica charantia* polysaccharides inhibit JNK3 induced cerebral injury by means of its antioxidant activities³⁷. A steroidal saponin isolated from *Momordica cymbalaria Fenzl (Cucurbitaceae)* produced a potential neuroprotective compound which enhanced the neuronal degenerative changes³⁸. It has been stated that β -carotene, a compound from *Moringa oleifera Lam. (Moringaceae)* will promote neuritogenesis³⁹. Chun *et al.*, reported the neuroprotective effect of macelignan isolated from *Myristica fragrans Houtt. (Myristicaceae)* which significantly reduced the spatial memory impairment induced by the chronic lipopolysaccharide infusions. The results add that the macelignan may target therapeutic compounds to prevent Alzheimer's disease⁴⁰⁻⁴¹. The neuroprotectivity and anti-depressant effect of luteolin, carnosic acid, rosmarinic acid and polyphenol compound from *Rosmarinus officinalis (R. officinalis)* has been reported⁴². The anticonvulsant and anxiogenic activity of triterpene isolated from *Rubia cordifolia Linn (Rubiaceae)* and the possibility of its anticonvulsant activity is mediated by chloride channels of GABA/benzodiazepine receptor complex instead of the chloride channel of glycine receptors of rat brain is a recent study in this area⁴³. Another report pointed out that the polysaccharides from *Rubia cordifolia* enhanced the proteasome activity which inhibited A β aggregates⁴⁴. The active constituents from *Solanum nigrum* suppressed free radicals in the brain which are under psychological stress and neuronal diseases⁴⁵. The neuronal protectivity of arjunolic acid from *Terminalia arjuna Weight & Arn. (combretaceae)* against oxidative stress induced damage in focal cerebral ischemia and reperfusion has been identified⁴⁶. Chebulic acid has been isolated from *Terminalia chebula Retzius (Combretaceae)* which was demonstrated to have a potential active compound against the AGE-induced endothelial cell dysfunction⁴⁷. These endothelial cell dysfunction inhibition activities were necessary in case of Alzheimer disease stage. Since, recently it was reported that Alzheimer disease may process endothelial dysfunction in its pathogenesis stage⁴⁸. Reports on bacopaside I from *Bacopamonnieri (L.) Wettst* which exhibited a potential neuroprotective effect against OGD-induced neuronal cell damage by means of blocking the PKC inhibitor Ro-31-8220 and P13K inhibitor in mouse model has been referred⁴⁹. Another report supports the presence of anti-stress agents like bacopaside I by means of stimulating antioxidant activity in adverse stress conditions in rat brain⁵⁰. The acetylcholine esterase inhibiting activity of Huperzine A, an alkaloid from *Huperzia serrata (Lycopodiaceae)* is a recent report from pharmaceutical scientists⁵¹. A report on Huperzine A suggests that it can be a potential therapeutic compound to overcome the Alzheimer's disease⁵². The potentiality of crocin from *Crocus sativus L.* has revealed to boost the memory through inhibition of the oxidative stress inducing neuronal damage⁵³. The anticonvulsant activity of morusin isolated from *Morusalba L* was demonstrated⁵⁴. Another report points out that the neuroprotective effect of cyaniding-3-O- β -D-glycopyranoside isolated from *Morusalba L.* revealed a neuroprotective effect on the PC12 and cerebral

ischemic damage by means of its antioxidant activities⁵⁵. The anti-stress activity of ocimumosides A, B and ocimarine isolated from *Ocimum sanctum* which normalizes the hyperglycemia, corticosterone levels, creatine kinase and adrenal hypertrophy effects is an already proven experimental methodology⁵⁶. The anti-depression and anti-anxiety effects of glycol-withanolides from *Withania somnifera (L.) Dunal* has been considered as an important information⁵⁷. Another experimental study on sitoindosides IX and X compounds from *Withania somnifera (L.)* showed its potential anti-stress nature which had an enhancing learning and memory retention in rat⁵⁸.

STANDARDIZED EXTRACT FROM HERBS

CURCUMA LONGA L.

The enhancement of learning and spatial memory by the compounds from *Curcuma longa. L* was reported by Nam sung *et al.*, at the dosage levels of 300 mg/Kg through oral administration in the adult mice⁵⁹.

ACORUS CALAMUS LINN

Acorus calamus Linn belongs to the family *Acoraceae*, a common ethno pharmacological plant widely used in Indian traditional based medicinal system such as Ayurveda, Unani, Siddha and also in Chinese medicine to treat various diseases and disorders including depression⁶⁰. The neuroprotective effect of ethanol: water (1:1) extract of rhizomes of *Acorus calamus* against cerebral ischemia was described elsewhere⁶¹. The neuro-modulatory effect of methanol and acetone extracts of *Acorus calamus* in mice was reported earlier⁶². Another report suggests that the oral and intraperitoneal injection (100 mg/kg) of *Acorus calamus* extracts enhance the spatial recognition and memory in male rats⁶³. Reports on the anti-cholinergic and anti-histaminic effect of *Acorus calamus* leaf extract is available in literature⁶⁴.

PIPER NIGRUM L

Piper nigrum L belongs to family *Piperaceae* which is a well-known medicinal plant for its antioxidant, anti-inflammatory, anti-hypertension and anti-depressant activity⁶⁵⁻⁶⁶. Reports on the anti-oxidative stress and neurodegenerative activity of methanol extracts of *Piper nigrum* seeds in Alzheimer induced rat are available with experimentation proof⁶⁷. Another report suggests the anti-neuro inflammatory like activity of *piper nigrum* alcoholic extract in Alzheimer induced rat⁶⁸. A recent, report on the memory enhancing activity of methanolic extracts of *piper nigrum* fruit by means of inhibiting the oxidative stress in Alzheimer rat model is available⁶⁹. The methanolic extract of *Piper nigrum* fruit extract showed possible anxiolytic and antidepressant activity in Alzheimer rat model⁷⁰.

CONVOLVULUS CHOISY

The plant belongs to the family *Convolvulaceae*. It is widely used in traditional Ayurveda and Chinese medicine to treat central nervous system and epileptic diseases⁷¹. Earlier reports suggest that the ethanolic extracts of *Convolvulus pluricaulis* enhance the learning and memory in young and aged mice at the dosage (200 mg/kg)⁷². Another report by Syed et al., suggest that *C. pluricaulis* extract at dosage (150 mg/kg) can inhibit amyloid β (A β) and increased amyloid precursor protein (A β PP) level in rat⁷³.

PSIDIUM GUAJAVA (L.)

P. guajava comes under the family *Myrtaceae*. The medicinal values of *P. guajava* are noted to treat inflammation, diabetes and central nervous system depressant activity⁷⁴. The ethanolic extracts of *P. guajava* showed significant impact in behavioral activity like locomotion and memory retention in obsessive compulsive disorder mice⁷⁵. Another recent experimental studies shows the potential antiepileptic activity of ethanol extract of *P. guajava* in mice (400 mg/kg)⁷⁶.

GLYCYRRHIZA GLABRA LINN

Belonging to the family *Leguminosae*, it is a common medicinal herb from the Indian medicinal history of Ayurveda to cure various diseases including hyperdipsia, inflammation and also in the treatment of epilepsy and paralysis⁷⁷⁻⁷⁸. The learning and memory enhancing effect of aqueous extract root of *G. glabra* was reported in experimental rat at 150 mg/kg dosage administered orally⁷⁹. Another recent experimental report suggests that the *G. glabra* will be the source of potential drug for Alzheimer and other neurodegenerative disorders. In this, the aqueous *G. glabra* root extract at the dosage 150 and 225 mg/kg significantly improve the learning and memory in male rats⁸⁰.

TINOSPORA CORDIFOLIA (LOUR.) MERR

Belonging to the family *Menispermaceae*, there has been several reports on the pharmacological activity of this plant including anti-inflammatory, anti-oxidant and anti-stress properties⁸¹. The clinical reports were pointed on the *T. cordifolia* tonic which can significantly improve behavior disorders and memory enhancing in children⁸². Another clinical study with thirty healthy 18-30 year volunteers showed 500 mg of pure aqueous *T. cordifolia* extract significantly increase verbal learning and memory behaviors⁸³. Reports on the ethanol and aqueous extracts of *T. cordifolia* can inhibit the cyclosporine induced memory deficit and enhance the learning and memory in rats⁸⁴. Another report suggests that anti-inflammation and antioxidant properties of *T. cordifolia* play an important role in memory enhancement process⁸⁵.

DAECALEPIS HAMILTONII WIGHT & ARN

The herb belongs to the family *Asclepiadaceae*. The root extract is considered as the major medicinal properties to cure epilepsy and central nervous system disorders⁸⁶. Several recent experiment studies reveals the antioxidant properties of *D. hamiltonii* as key responsible agent for its neurodegenerative activity. Reports on the root extract of *D. hamiltonii* reduces the age-related decline in cognitive ability in *Drosophila melanogaster* means of its antioxidant properties⁸⁷. A very recent report on the antioxidant properties of *D. hamiltonii* extract promisingly enhance the climbing ability and circadian rhythm of locomotor activity in *Drosophila melanogaster* model after feeding the extract for twenty one days has been evaluated⁸⁸. Suggestion on the antioxidant properties of *D. hamiltonii* root extract can play a major contribution for its neuroprotective activity⁸⁹.

SEMECARPUS ANACARDIUM LINN

Belonging to the family *Anacardiaceae*, it is well known for various ailments in traditional system. The fruits and nuts of *S. anacardium* are considered to add major medicinal value to treat inflammation, central nervous system disorders and hypoglycemic activity⁹⁰. An important report an ethanolic extract of *S. anacardium* inhibits the neuronal degenerative disorder induced by stress in experimental rats which resembles the cytoprotective properties has been evaluated⁹¹. A detailed description on the central nervous system effect of *S. anacardium* nuts milk extract shows that it can enhance the locomotory and nootropic activity in various animals models by inhibit AchE leads to improving the half-life of acetylcholine effectively and enhancing the memory process⁹².

FLEMINGIA STROBILIFERA L (R.BR)

The plant belongs to the family *Leguminosae*. The root parts are applied to treat epilepsy and hysteria⁹³. The tribal people from Assam use *F. strobilifera* to cure ringworm infection by applying over the infected area⁹⁴. Only a few experimental data was available on *F. strobilifera* which deals with the neuro-pharmacological activities. Reports on the anticonvulsant activity of ethanol extract of the roots of *F. strobilifera* and ethyl acetate fraction revealed depressant like action in central nervous system in locomotor activity without inhibiting the motor coordination at the dose (400 and 600 mg/kg)⁹⁵.

CINNAMOMUM TAMALA (BUCH-HAM) NEES AND E BERM

Belonging to *Lauraceae* family, it was applied to treat various diseases and infection in the traditional medicinal system of Ayurveda and Yunani. Several experimental studies states its potential properties such

as anti-diabetics, anti-inflammation, anti-cancer and anti-oxidant activities properties⁹⁶. Recently, reports on the acetylcholinesterase inhibition activity of *C. tamala* methanol extract and its leaf oil cinnamon are available. Among this, cinnamon oil shows maximum acetylcholinesterase inhibition than the *C. tamala* extract⁹⁷.

CYPERUS ROTUNDUS

The plant belongs to the family *Cyperaceae*. It is well known for its traditional medicinal value to treat analgesic, malarial infection and inflammation⁹⁸. Several recent experimental data suggest that its free radical scavenging activity leads to neuroprotective properties. Reports are available on the neuroprotective effect of *C. rotundus* extract against ONOO- induced apoptosis by inhibiting NO generation by down regulating i-NOS expression⁹⁹. Same as the previous report, description on the neuroprotective activity of *C. rotundus* rhizome extracts through inhibiting H₂O₂ induced human neuroblastoma cell damage which increases the brain derived nerve growth factor resembling its neuro-regeneration properties has been proved by experimentation¹⁰⁰. Another recent experimental study on Alzheimer animal model suggests the learning and memory enhancing activity of *C. rotundus* tubers ethanolic extract. In this *C. rotundus* extract potentially inhibiting the loss of cholinergic neurons of the nucleus basalis of meynert which leads to overcome Alzheimer disorders in animal models¹⁰¹.

CENTELLA ASIATICA (L.) URBAN

Belonging to the family *Apiaceae*, *C. asiatica* traditionally is well known for its memory enhancement and also for neurological medicinal properties in many countries¹⁰². Reports on the inhibition of streptozotocin induced cognitive impairment in the Alzheimer model treated with 200 and 300 mg/kg of aqueous extract of *C. asiatica* is an effective means of suppressing the oxidative stress¹⁰³. Another report also suggests that *C. asiatica* extract shows significant neuroprotective in age related disorders by inhibiting lipid peroxidation and protein carbonyl in aged rat brain¹⁰⁴. A report on solvent of n-hexane, chloroform, ethyl acetate and n-butanol extract of *C. asiatica* shows increased in ATPases in different regions of rat brain epilepsy¹⁰⁵. A very recent report suggests that *C. asiatica* extract significantly inhibit the thiol oxidation induced by sodium nitroprusside and quinolinic acid in different regions of brain¹⁰⁶. Another experimental study suggests ethanolic extract of *C. asiatica* possess anti-oxidant defense mechanism to inhibit A β ₁₋₄₀ induced reactive oxygen species free radicals neurotoxicity in Alzheimer condition¹⁰⁷.

EMBELIA RIBES BURM.F

Belonging to the *Myrsinaceae* family, the dried fruits of *E. ribes* were used to treat helminthic, carminative and

inflammation¹⁰⁸. Reports on the neuroprotective effect of *E. ribes* ethanol extract which inhibits the oxidative stress in middle cerebral artery occlusion leads to focal cerebral ischemia in rats¹⁰⁹.

AERUALANATA (L.) JUSS. EXSCHULT

Belonging to the family *Amaranthaceae*, the plant is widely used in traditional system of medicine to cure helminthic, inflammation, skin diseases and headache¹¹⁰. Very recently, reports on the neuroprotective effect of *A. lanata* 70% ethanolic extracts against cisplatin induced neurotoxicity in male rats has been observed¹¹¹.

MANGIFERA INDICA L.

The tree belongs to the family *Anacardiaceae* and the ethno-pharmacological importance of *M. indica* has been reported to treat diarrhea, jaundice, pain and inflammations. The extracts which proved to have free sugars, saponin, tannins and flavonoids when treated chronically with vitamin C on mice reversed aging and memory deficits and hence suggests to contain memory enhancing pharmacologically active principles¹¹².

CONCLUSIONS

Alzheimer's the multifactorial complex disease which is a type of dementia causing mental disability and death among humans. Current therapy can relieve the symptoms of the disease and cannot prevent the progression as it uses acetylcholine esterase inhibitors. Hence use of bioactive agents derived from Indian traditional ayurvedic medicines have multi-targeted agents for therapy so as to specifically bind and deactivate the preformed complexes. These multifaceted drugs have to be structurally characterized and their pharmacokinetic activities are to be routed in order to establish the structure - activity relationship studies of individual compounds present in herbal complexes. More attention is required towards their derivatives and tissue restoration processes. Studies should be undertaken to overcome the clinical hurdles currently faced by the herbal drugs such as brain penetration and oral activities.

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CONFLICT OF INTEREST

Conflict of interest declared none.

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