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

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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

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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 problems. 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 diseases. 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 disease. The development of traditional based medicine mainly focused on three approaches such as isolated single compound, poly-herbal mixture and pharmaceutical 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 compounds. 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 has been suggested to play a major role in ageing and neurodegenerative diseases by means of increase dopamine oxidation in nigral dopaminergic neurons. 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 oxidation. 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 Alzheimer. 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 βA(1-42) through antioxidant pathway. Nongnut et al., described the saponins and glycosides isolated from perennial creeping plant Bacopama niera Linn. which exhibited lipid peroxidation inhibitory activity and neuroprotection against Alzheimer disease. A flavonoid kaempferol isolated from Ginkgo biloba leaves were potentially neuro-protectant as described elsewhere. The inhibition of noise stress induced changes in the rat brain was determined by a novel drug α-asarone from Acorus calamus. Gabrind isolated from Glycyrrhiza glabra (liquorice) showed neuroprotective effect on pathways associated with an apoptosis. Reports are available on arabinogalactan polysaccharide isolated from Tinospora cordifolia (Menispermaceae) which revealed protection against iron-mediated lipid peroxidation in rat brain cellular glutathione. The neuroprotective compound FrB from convolvulus Pluricaulis choi. (Convolvulaceae) stimulates the antioxidant mechanism in brain has been reported. 4-hydroxyisophthalic acid an antioxidant compound isolated from Decalepis hamiltonii roots are reported as neuroprotective agent. An acetylcholinesterase (AChE) inhibitor compound catechol alkenyls from Semecarpus anacardium L. f. (Anacardiaceae) was reported in earlier studies. The saponin rich fraction of Ficusreligiosa L. (Moraceae) showed anticonvulsant activity against epileptic seizures induced synchronous neuronal activity in the brain has been reported earlier. The anti-depressant activity in mouse brain monoamine neurotransmitters by means of reduced monoamine oxidase (MAO)-A level has been demonstrated. Another compound iso-curcumenol from Cyperus rotundus L. (Cyperaceae) acts as a benzodiazepine receptor against an allosterically modulated GABAergic neurotransmission. The asiatican triterpenoid and madecassic acid from Centella asiatica urban (Umbelliferae) were reported as neuro protective agent. 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 receptor and also due to its antioxidant properties was studied. 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-β activity. A patent compound vicenin-2 was reported for its potential neurological activity to control Alzheimer. It was stated that the acetylcholinesterase (AChE) inhibiting nature of coumarin isolated from Lantana camara (Verbenaceae). 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 components. 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 cleft. 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 described. Another recent experimental study suggests that Momordica charantia polysaccharides inhibit JNK3 induced cerebral injury by means of its antioxidant activities. A steroidal saponin isolated from Momordica cymbalaria Fenzl (Cucurbitaceae) produced a potential neuroprotective compound which enhanced the neuronal degenerative changes. It has been stated that β-carotene, a compound from Moringa oleifera Lam. (Moringaceae) will promote neuritogenesis. 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 disease. The neuroprotectivity and anti-depressant effect of luteolin, carnosic acid, rosmarinic acid and polyphenol compound from Rosmarinus officinalis (R. officinalis) has been reported. 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 area. Another report pointed out that the polysaccharides from Rubia cordifolia enhances the proteasome activity which inhibited Aβ aggregates. The active constituents from Solanum nigrum suppressed free radicals in the brain which are under psychological stress and neuronal diseases. The neuronal protective activity of arjunolic acid from Terminalia arjuna Weight & Am. (combretaceae) against oxidative stress induced damage in focal cerebral ischemia and reperfusion has been identified. Chebulic acid has been isolated from Terminalia chebula Retzis (Combretaceae) which was demonstrated to have a potential active compound against the AGE-induced endothelial cell dysfunction. 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 stage. Reports on bacopaside I from Bacopamonnieri (L.) Wattst 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 referred. Another report supports the presence of anti-stress agents like bacopaside I by means of stimulating antioxidant activity in adverse stress conditions in rat brain. The acetylcholine esterase inhibiting activity of Huperzine A, an alkaloid from Huperzia serrata (Lycopodiaceae) is a recent report from pharmaceutical scientists. A report on Huperzine A suggests that it can be a potential therapeutic compound to overcome the Alzheimer’s disease. The potentiality of crocin from Crocus sativus L. has revealed to boost the memory through inhibition of the oxidative stress inducing neuronal damage. The anticonvulsant activity of morusin isolated from Morusalba L was demonstrated. Another report points out that the neuroprotective effect of cyaniding-3-O-β-D-glycosyranoside isolated from Morusalba L. revealed a neuroprotective effect on the PC12 and cerebral ischemic damage by means of its antioxidant activities. The anti-stress activity of ocimunosides 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 methodology. The anti-depression and anti-anxiety effects of glycol- withanolides from Withania somnifera (L.) Dunal has been considered as an important information. 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 rat.

**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 mice.

**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 depression. The neuroprotective effect of ethanol: water (1:1) extract of rhizomes of Acorus calamus against cerebral ischemia was described elsewhere. The neuro-modulatory effect of methanol and acetone extracts of Acorus calamus in mice was reported earlier. Another report suggests that the oral and intraperitoneal injection (100 mg/kg) of Acorus calamus extracts enhance the spatial recognition and memory in male rats. Reports on the anti-cholinergic and anti-histaminic effect of Acorus calamus leaf extract is available in literature.

**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 activity. Reports on the anti-oxidative stress and neurodegenerative activity of methanol extracts of Piper nigrum seeds in Alzheimer induced rat are available with experimentation proof. Another report suggests the anti-neuro inflammatory like activity of piper nigrum alcoholic extract in Alzheimer induced rat. 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 available. The methanolic extract of Piper nigrum fruit extract showed possible anxiolytic and antidepressant activity in Alzheimer rat model.
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 diseases. Earlier reports suggest that the ethanolic extracts of *Convulvulus pluricaulis* enhance the learning and memory in young and aged mice at the dosage (200 mg/kg). Another report by Syed et al., suggest that *C. pluricaulis* extract at dosage (150 mg/kg) can inhibit amyloid β (Aβ) and increased amyloid precursor protein (AβPP) level in rat.

PSIDIIUM GUAVA L.

*P. guava* comes under the family Myrtaceae. The medicinal values of *P. guavarae* noted to treat inflammation, diabetes and central nervous system depressant activity. The ethanolic extracts of *P. guava* showed significant impact in behavioral activity like locomotion and memory retention in obsessive compulsive disorder mice. Another recent experimental studies shows the potential antiepileptic activity of ethanol extract of *P. guava* in mice.

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 hyperlipidemia, inflammation and also in the treatment of epilepsy and paralysis. The learning and memory enhancing effect of aqueous extract root of *G. glabra* was reported in experimental rat at 150 mg/kg dosage administered orally. 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 rats.

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 properties. The clinical reports were pointed on the *T. cordifolia* tonic which can significantly improve behavior disorders and memory enhancing in children. 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 behaviors. Reports on the ethanol and aqueous extracts of *T. cordifolia* can inhibit the cyclosporine induced memory deficit and enhance the learning and memory in rats. Another report suggests that anti-inflammation and antioxidant properties of *T. cordifolia* play an important role in memory enhancement process.

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 disorders. 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 properties. A very recent report on the antioxidant properties of *D. hamiltonii* extract promisingly enhance the climbing ability and circadian rhythm of locomotors activity in *Drosophila melanogaster* model after feeding the extract for twenty one days has been evaluated. Suggestion on the antioxidant properties of *D. hamiltonii* root extract can play a major contribution for its neuroprotective activity.

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 activity. 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 evaluated. 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 process.

FLEMINGIA STROBILIFERA L (R.BR)

The plant belongs to the family Leguminosae. The root parts are applied to treat epilepsy and hysteria. The tribal people from Assam use *F. strobilifera* to cure ringworm infection by applying over the infected area. 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).

CINNAMOMUM TAMALA (BUCH-HAM) NEES AND E BERM

Belonging to Lauraeae 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 properties. 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 traditionally is well known for its memory enhancement carbonyl in aged rat brain extract shows significant neuroprotective in age related disorders by inhibiting lipid peroxidation and protein. Suggests that the acetylcholinesterase inhibition activity of neurotoxicity in Alzheimer condition induced reactive oxygen species free radicals experimentation. 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 models.

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 countries. 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 stress. 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 brain. 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 epilepsy. 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 brain. Another experimental study suggests ethanolic extract of C. asiatica possess anti-oxidant defense mechanism to inhibit Aβ1-40 induced reactive oxygen species free radicals neurotoxicity in Alzheimer condition.

EMBELIA RIBES BURM.F

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

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 headache. Very recently, reports on the neuroprotective effect of A. lanata 70% ethanolic extracts against cisplatin induced neurotoxicity in male rats has been observed.

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 principles.

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.
REFERENCES


46. Yaidikar L, Thakur S. Arjunolic acid, a pentacyclic triterpenoidal saponin of Terminalia arjuna bark protects neurons from oxidative stress associated damage in focal cerebral ischemia and reperfusion. Pharmacological Reports. 2015 Oct 31;67(5):890-5.
50. Chowdhuri DK, Parmar D, Kakkar P, Shukla R, Seth PK, Srimal RC. Antistress effects of bacosides of Bacopa monnieri: modulation of...


Rabiei Z, Hojjati M, Rafieian-Kopaeia M, Albabaei Z. Effect of Cyperus rotundus tubers ethanolic extract on learning and memory in animal model...


