THE NEUROPROTECTIVE EFFECTS OF MEDICINAL PLANTS ON ALZHEIMER`S DISEASE: A REVIEW

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AUTHORS' CONTRIBUTIONS

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

> *Review Article*

ABSTRACT

In the 21st century, the human population is suffering from a neurodegenerative disorder in which neuronal death occurs due to a long-term chronic condition causing substantial major health concerns. When neurons die, they are not regenerated, causing cognitive impairment, i.e., Alzheimer's disease, Parkinson's disease, schizophrenia, and dementia. This review concentrates only on Alzheimer's disease aetiology and various plants having potent neuroprotective activity related to Alzheimer's disease. The most common aetiology of Alzheimer's disease is a deposition of APP protein, hyperphosphorylation of Tau protein, a reduction in acetylcholine and oxidative stress, which are discussed briefly. Moreover, pertinent evidence is also discussed for medicinal plants with potent or promising neuroprotective activity related to Alzheimer's disease.

Keywords: Alzheimer's disease; *Bacopa monnieri*; neuroprotective; pathophysiology; *withania somnifera*.

1. INTRODUCTION

The medicinal plant comprises a set of plants used in plant-based herbal remedies for medical treatment, most of which have therapeutic qualities [1]. In past decades, humans relied heavily on the healing properties of medicinal plants before the introduction of allopathic medicines. Some people regard these plants as beneficial because of an ancient belief that plants were created to provide man with food, medical treatment, and other economic advantages [2]. Because of its minimal side effects, cheap and locally available, 70% of the global population depends upon herbs for medicine [3].

Neurodegenerative diseases (ND) are disorders characterized by the selective loss of neurons that pose a significant risk to human health. These are age- related disorders that are becoming more common. Some neurodegenerative disorders include Alzheimer's disease, Huntington's disease, Parkinson's disease, amyotrophic lateral sclerosis, and spinocerebellar ataxia [4]. This review mainly focused on medicinal plants having potent neuroprotective activity related to Alzheimer's disease (AD).

Alzheimer's disease (AD) is a neurodegenerative disease that is the most common type of dementia, accounting for approximately 60-80% of all cases [5]. In 1901, a 51-year-old woman named Auguste Deter was diagnosed with her first Alzheimer's disease [6]. *Alzheimer's disease* is an irreversible age-related neurodegenerative disorder that depletes brain size and causes neuronal death in the basal forebrain and hippocampus [7]. It manifests as memory deficits and

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cognitive decline, learning and memory dysfunction, communication sequence disorientation, and mood swings [8,9]. In 2021, 6.2 million Americans age 65 and older were living with Alzheimer's dementia, and it is projected that 12.7 million will have Alzheimer's dementia by 2050 [10]. In 2013, out of 1000 people, 33 people were affected by Alzheimer's disease, and about 37 lakh people in India were affected by Alzheimer's disease. It is estimated that the number of affected people will double by 2030 [11].

2. PATHOPHYSIOLOGY OF ALZHEIM-ER'S DISEASE

The pathogenesis of AD is unknown; however, some possible mechanisms (Fig.1) are reported; they are: Due to long-prolonged exposure to heavy metals, stress, hypertension, genetic factors, lifestyles and history of head injuries but there is no clear hypothesis [12-14].

Amyloid-beta precursor protein (APP) is present in the cell membrane as a transmembrane protein having intracellular and extracellular components. It has cleavage sites for α, β, and γ-secretase enzymes. α and β-secretase cleavage sites are present on the cell's surface, while γ-secretase has a cleavage site in the intramembranous region of the protein. Typically cleavage by α-secretase is followed by cleavage by γ-secretase, which results in the formation of soluble protein. In an AD patient, β-secretase does the first cleavage, which is followed by cleavage by γ-secretase resulting in the generation of Aβ protein

which gets aggregated and gets deposited in various parts of the brain [15].

Tau proteins are present in brain cells, which is a microtubule-associated protein (MAP) which stabilizes microtubules. Hyperphosphorylation of these proteins may result in aggregation to form neurofibrillary tangles, which results in disruption of neuronal signaling and programmed cell death [16].

The cholinergic theory hypothesizes that cholinergic system dysfunction contributes to cognitive decline. One of the biomarkers of Alzheimer's disease is decreased acetylcholine (ACh) concentration and function, which is associated with memory and learning [17].

High levels of reactive oxygen species, or oxidative stress, are acknowledged as a negative factor in developing Alzheimer's disease. It is widely accepted that oxidative stress in the frontal cortex plays a role in cognitive impairment [18]. Because the human brain requires more energy than other tissues, it consumes more oxygen, raising the risk of tissue damage and free radicals [19]. Glutathione, the most common endogenous antioxidant in the brain, can eliminate excessive reactive oxygen levels (ROS) in normal conditions. Glutathione deprivation is a contributing factor to hippocampus and frontal cortex damage [20]. In addition, ROS promotes lipid, protein, and nucleic acid oxidation in neurons and the deposition of amyloid beta and hyperphosphorylated tau protein in neurons [21].
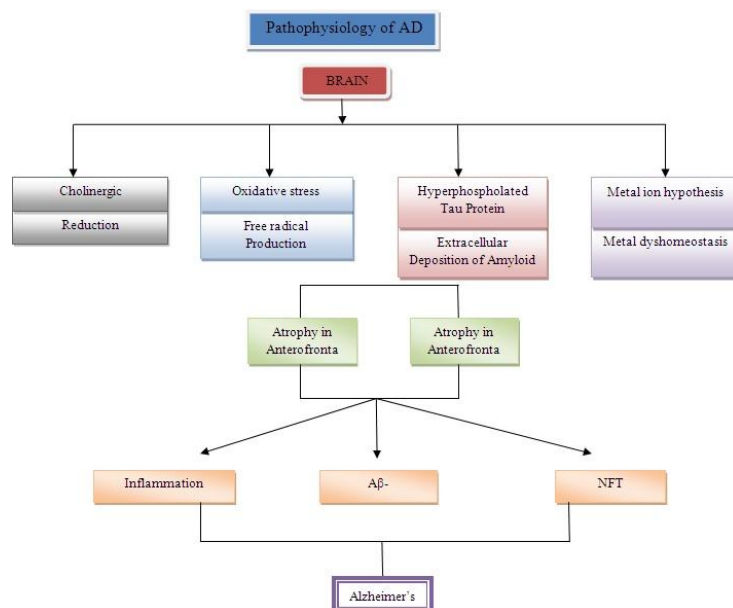

Fig. 1. Pathophysiology of Alzheimer's disease

Chronic inflammation is also one possible pathogenesis of AD. Inflammation may be provoked by β-amyloid deposits, NFTs, and damaged neurons as a natural response to cell damage. Microglia (one of four types of brain cells, together with neurons, astrocytes, and oligodendrocytes) play a role in immune and inflammatory responses to injury or infection in the brain. Microglias are activated during AD pathogenesis and release cytotoxic molecules such as proteinases, complement proteins, pro-inflammatory cytokines, and reactive oxygen species. It is a normal response to cellular damage that appears uninhibited in Alzheimer's disease, causing more harm than protection [22].

3. MEDICINAL PLANTS HAVING POTENT ANTI-ALZHEIMER'S ACTIVITY

Abrus precatorius

Abrus precatorius, commonly known as "Chanoti," belongs to Fabaceae. Tribal peoples have used it in folkloric medicine for many years, and it is said to have a wide range of therapeutic effects like antitumor, antifungal, analgesic, antibacterial, antidiabetic, neuroprotective, anti-inflammatory, and many more. In certain tribal areas, people chew the leaves of *A. precatorius* to relieve mouth ulcers [23].

Choudhary GP et al., investigated *the* neuroprotective activity of methanolic leaf extract of *A. precatorius* in scopolamine induced mice. The extract at a 300 mg/kg dose proved to have marked neuroprotective activity. The possible mechanism is that the study of memory building relies heavily on changes in the extracellular level of neurotransmitters in CNS areas involved in information transmission and regulation [24].

Aegle marmelos

Aegle marmelos, commonly known as Bael (Hindhi) and Bilpatra (Kannada), belong to the Rutaceae. The fruits and leaves of this plant have more health benefits than other aerial parts. It has several primary clinical uses, like anti-inflammatory, antifungal, wound healing properties, hypoglycemic, anticancer, antipyretic, neuroprotective, anti-lipidemic, and many more [25].

Ramakrishna Y.G. et al. investigated the neuroprotective activity of ethanolic leaf extracts of *A. marmelos* in streptozotocin-induced rats. The extract at a dose of 200 and 400 mg/kg proved to have marked neuroprotective activity [26].

Kumar P et al. investigated the neuroprotective activity of methanolic leaf extract (MLE) and methanolic fruit extract (MFE) of *A. marmelos* in albino rats. The extract at a dose of 100 and 200 mg/kg, both MLE and MFE, proved to have marked neuroprotective activity [27].

Allium sativum

Allium sativum plant, commonly known as Lasuna, Rosona (Sanskrit), Garlic (English), Lashan (Hindhi), Bellulli (Kannada), belongs to the family Amaryllidaceae. From ancient times, A. sativum has been used as a medicinal herb containing phytochemicals directly linked to many activities like anti-diabetic, hepatoprotective, anti-inflammatory, neuroprotective, antifungal, anticancer, antibacterial, immunomodulatory, anti-obesity, and many more. So it is concluded that garlic is one of the best natural sources of antioxidants, with potential applications in the development of functional foods and nutraceuticals to improve human health and prevent chronic diseases [28].

Jeong JH *et al. investigated the* neuroprotective activity of an ethanolic extract partitioned with n-hexane, chloroform, ethyl acetate, and water of *A. sativum* in ICR mice. At doses of 5, 10, and 20 mg/kg, the ethyl acetate fraction proved to have marked neuroprotective activity. An in-vitro test was also carried out using PC12 cell culture [29].

Bacopa monnieri

Bacopa monnieri plant commonly known as Brahmi belongs to the family Scrophulariaceae. Brahmi is considered as a powerful brain or nerve tonic which plays an important role in memory booster or nootropics. Brahmi also contain many pharmacology related activites like tranquilizer, diuretic, sedatives, cardio-tonic, antistress and many more [30].

Uabundit N et al. investigated neuroprotective activity of ethanolic extract of aerial parts of *B. monnieri* in male wistar rats. The extract at a dose of 20, 40 and 80 mg/kg proved marked neuroprotective activity [31]. The neuroprotective activity is due to presence of "Bacosides A & B [32].

Centella asiatica

Centella asiatica plant commonly known as Indian pennywort, jalbrahmi and mandookaparni belongs to the family Umbellifere (Apiceae). In indian system of medicine, C. asiatica plays an important role as

memory enhancer, treatment in nervine disorder and skin related diseases [33]. Also this plant related to various pharmacological activities like wound healing, antitumour, immunomodulatory, hepatoprotective, cardioprotective, antidepressant, antiviral, anti-inflammatory and many more [33].

Rahman MM et al. investigated invitro neuroprotective activity by quantifying acetylcholinesterase and butyrylcholinesterase enzyme. The ethanloic leaves extract of *C. asiatica* showed significant AchE and BchE inhibitory effect [34].

Celastrus paniculatus

In ayurveda, the plant *Celastrus paniculatus* is called as a "Tree of life" belongs to the family Celastraceae which plays an important role in learning and memory enhancement [35]. *C. paniculatus* also known as Kariganne(Kannada), Staff tree(English), alkangani(Hindi). The seeds of this plant have numerous pharmacological factors like appetizer, stimulant, cardiotonic, nootropic activity, anti-inflammatory activity, laxative, aphrodisiac, diuretic etc. The bark is considered as a powerful brain tonic [36].

Badrul A et al. investigated invitro anti-alzheimer's activity by quantifying AchE and BchE enzyme. The methanolic seed extract of *C. paniculatus* showed significant AchE and BchE inhibitory effect [37].

Coriandrum sativum

Coriandrum sativum is commonly known as Dhanya, coriander belongs to the family Umbelliferae. It is an unripe fruit with very pungent odour. The leaves of these plants are used in cooking contain many medicinal properties. Coriander has many numerous pharmacological properties like antidiabetic, diuretic, hepatoprotective, anticancer, anti-ulcer, anti-mutagenic, anticonvulsant, anxiolytic, sedative and hypnotic activity and many more [38].

Elahdadi-Salmani M et al. investigated neuroprotective activity of ethanolic leaves extract of *C. sativum* against epilepsy induced learning and memory deficits in male wistar rats. The extract at the dose of 200 mg/kg proved marked neuroprotective activity [39].

Crocus sativus

Crocus sativus plant also known as Kesari(Kannada), Saffron(English), Zaafraan, Kesar(Hindhi) belongs to the family Iridaceae. *C. sativus* related to various pharmacological activites like antidiabetic, memory enhancer, anticancer, antianxiety, analgesic, antidepressant, smooth muscle relaxation, anti-inflammatory and many more [40].

Khalili M et al. investigated neuroprotective activity of chief active constituent crocin present in the *C. sativus* against streptozocin induced cognitive impairement in male wistar rats. The crocin at a dose of 30mg/kg proved marked neuroprotective activity [41].

Curcuma longa

Curcuma longa is commonly known as Haldi or turmeric belongs to the family Zingiberaceae. This plant is holistic gift of nature to human world in the field of cosmetics as well as medication also. It has numerous pharmacological activities like hepatoprotective, anti-depressant, anti-inflammatory, anti-fertility, anti-oxidant, neuroprotective, chemoprotective, anti-microbial, HIV-1 & HIV-2 protease inhibitor and many more [42].

Lohit K et al. investigated neuroprotective activity of aqueous extract of powdered rhizome of *C. longa* in albino wistar rats. The extract at a dose of 10 and 50 mg/kg proved marked neuroprotective activity [43].

Eclipta prostrata

Eclipta prostrata is commonly known as Bhringraj(Ayurveda), false daisy(English) belongs to the family Compositae. It is a conventional herbal based medicinal plants used from hundreds of years ago in Asia and south America for the prevention of many hemorrhagic diseases, respiratory disorders, heart related diseases, skin diseases etc. It has many promising pharmacological activites like neuroprotective; promote hair growth hepatoprotective, cytotoxic, anti-microbial, antidiabetic, anti-inflammatory, hypolipidemic and many more [44].

Jung WY et al. investigated neuroprotective activity of ethanolic plant extract *E. prostrate* against scopolamine induced memory impairment in male ICR mice. The extract at a dose of 50 and 100 mg/kg proved marked neuroprotective activity [45].

Enhydra fluctuans

Enhydra fluctuans is commonly known as Marsh herb, buffalo spinach, water cress belongs to the family Asteraceae. It has a huge potential as a medicinal plant, as well as a lot of beneficial effects like neuroprotective, anti-inflammatory, antidiabetic,

antimicrobial, anticancer, hepatoprotective and many more [46].

Lopa SS et al. investigated invitro neuroprotective activity by quantifying acetylcholinesterase and butyrylcholinesterase enzyme. The chloroform extract of stems and leaves of *C. asiatica* showed significant AchE and BchE inhibitory effect [47].

Ferula asafoetida

Ferula asafoetida commonly known as hingu in india belongs to the family Umbelliferae which is a oleo-gum resin with very strong and sulfurous odour with many promising medicinal activites like neuroprotective, antispasmodic, hepatoprotective, digestive enzyme, antimicrobial, anthelmintic, anticarcinogenic, hypotensive, anticancer and many more [48].

Vijayalakshmi SA et al. investigated neuroprotective activity of aqueous gum extract of *F. asafoetida* in male wistar rats. The extract at a dose of 400 mg/kg proved marked neuroprotective activity [49].

Ginkgo biloba

Ginkgo biloba is commonly known as Fossil tree, Kew tree, Maidenhair tree belongs to the family Ginkgoaceae. Since more than 2000 years, *G. biloba* has been regarded as a vital plant for mankind. It has various pharmacological activities like hepatoprotective, antioxidant, antidiabetic, antibacterial, anti-inflammatory, antifungal, neuroprotective, antidepressant, anticancer and many more [50].

Ge W et al. investigated neuroprotective activity of *G. biloba* extract (EGb 761) against 5×FAD transgenic mice. The EGb 761 at a dose of 20 & 30 mg/kg protects against memory deficits in 5×FAD mice [51].

Glycyrrhiza glabra

Glycyrrhiza glabra is commonly known as Liquorice(English), Yastimadhuka, atimaddhura (Kannada), Mulhatti(Hindhi) belongs to the family Leguminosae. Egyptian, Chinese, Greek, Indian, and Roman civilizations used the dried rhizome and root of this plant as an expectorant and carminative. *G. glabra* contains numerous pharmacological activites like antimalarial, anti- inflammatory, antioxidant, antiviral, antidiabetic, antiulcer, neuroprotective, antispasmodic and many more [52]. Chakravarthi KK et al. investigated neuroprotective activity of aqueous root extract of *G. glabra* in wistar albino rats. At the

dose of 150 and 225 mg/kg proved marked neuroprotective activity [53]. The neuroprotective activity is due to the major active isoflavan "Glabridin" present in *G. glabra* [54].

Huperiza serrata

Huperiza serrata is commonly known as Chinese clubmoss belongs to the family Lycopodiaceae. It is a Chinese medicinal plant commonly known as *Qian Ceng Ta* which is a promising medicinal plant for neurodegenerative disorders. Apart from neuroprotective, it has many other pharmacological activites like anti-inflammatory, anti-apoptosis, anticonvulsant, anti-nociception and many more [55].

Ohba T et al. investigated neuroprotective activity of ethanolic plant extract of *H. serrata* against scopolamine induced cognitive impairment in mice. The extract at the dose of 30 mg/kg proved marked neuroprotective activity due to the presence of alkaloid Huperzine A [56].

Hypericum perforatum

Hypericum perforatum commonly known as St. john's wort belongs to the family Hyperiaceae. The plant has been recognized for its important biological and chemical perspectives, and ethnobotanical publications have reported its usage in the treatment of infectious disorders. It has numerous pharmacological activites like antibacterial, antifungal, antimicrobial, antidepressant, antiviral, wound-healing and many more [57].

Cao Z et al. investigated neuroprotective activity of methanolic extract of *H. perforatum* against aluminium chloride-induced Alzheimer's disease in male wistar rats. The extract at a dose of 150 and 300 mg/kg proved marked neuroprotective activity [58].

Morus alba

Morus alba is commonly known as Mullbery belongs to the family Moraceae. This plant is used to treat various diseases like edema, diabetes, asthma, nosebleeds, bronchitis, wound healing, insomnia etc. The fruits are used to treat various ailments like fatigue, nourish the blood, anemia, kidney related problems etc. It has numerous pharmacological properties like antistress, anticancer, anxiolytic, antimicrobial, anti-dopinergic, antimutagenic, immunomodulatory and many more [59].

Kuk EB et al. investigated invitro neuroprotective activity by quantifying acetylcholinesterase and butyrylcholinesterase enzyme of methanolic extract of root bark, leaves, branches and fruits of *M. alba*. The root bark of *M. alba* shows significant AchE and BchE inhibitory effect compared to leaves, branches and fruits [60].

Nigella sativa

Nigella sativa is commonly known as Black cumin, kalaunji, kalavanjika, ajaji, kalika belongs to the family Ranunculaceae. It is used from hundreds of years ago in various systems of medicine like Ayurveda, Tibb, Unani and siddha. It has numerous pharmacological activates like antitumour, neuroprotective, antidiabetic, gastroprotective, hepatoprotective, nephroprotective, anti-inflammatory, immunomodulatory, anticonvulsant, anxiolytic, diuretic, antibacterial, antifungal, anthelmintic, antioxytocic and many more [61].

Hosseini M et al. investigated neuroprotective activity of hydro-alcoholic extract of seeds of *N. sativa* against scopolamine-induced spatial memory impairment in male wistar rats. The extract at a dose of 400 mg/kg proved marked neuroprotective activity [62].

Ocimum sanctum

Ocimum sanctum is commonly known as Tulsi belongs to the family Lamiaceae. In ayurveda, it is used from thousands of years ago. Fresh juice or decoction of *O. sanctum* leaves has traditionally been used to boost health and treat many illnesses as referenced by ayurveda, the Indian system of medicine. It has numerous pharmacological properties like neuroprotective activity, antimicrobial, antidiabetic, antifungal, wound healing effect, anti-stress, anticonvulsant, anti-ulcer, radio-protective effect, antipyretic and many more [63].

Ragavendra M et al. investigated neuroprotective activity of methanolic leaves extract of *O. sanctum* against colchicine(i.c.v) induced cognitive impairment in male Charles-Foster rats. The extract at a dose of
200 mg/kg proved marked neuroprotective activity [64].

Ricinus communis

Ricinus communis is commonly known as castor plant belongs to the family Euphorbiaceae. It is well known plants for the treatment of fungicide, laxative, purgative etc. and also promising for many pharmacological properties like antiulcer, wound healing, neuroprotective, antidiabetic, antioxidant, hepatoprotective, CNS stimulant, antinociceptive, immunomodulatory, antifertility and many more [65].

Lee E et al. investigated neuroprotective activity of undecylenic acid (UDA) extracted from *R. communis* by inhibiting the μ-calpain. μ-calpain creates a bridge between Aβ and hyperphosphorylated tau-mediated pathways that is a major pathogensis of AD. The UDA inhibits μ-calpain with better cell permeability and proved marked neuroprotective activity [66].

Semecarpus anacardium

Semecarpus anacardium is commonly known as Ballataka or Bhilwa belongs to the family Anacardiaceae. It is well known plant for their medicinal properties from ancient system of medicines i.e., Ayurveda and siddha. It has numerous pharmacological properties like antiatherogenic, antioxidant, anti-inflammatory, anti-carcinogenic, antimicrobial, hypoglycemic, neuroprotective and many more [67].

Gouda SS et al. investigated neuroprotective activity of milk extract of nuts of *S. anacardium* against scopolamine, diazepam and electroshock induced cognitive impairement in albino mice. The extract at a dose of 150 and 225 mg/kg proved marked neuroprotective activity [68].

Terminalia chebula

Terminalia chebula is commonly known as black myroblans(English), harad(Hindhi) is commonly known as Combretaceae. Due to its remarkable healing properties *T. chebula* is known as "King of Medicine" in Tibet and constantly at the top of ayurveda material medica. It has numerous promising pharmacological properties like wound healing effect, antimicrobial, antihyperglycemic, antifungal, immunomodulatory, hypolipidemic, antiviral, renoprotective, hepatoprotective, antiulcer, antinociceptive and many more [69].

Rao SN et al. investigated neuroprotective activity of ethanolic dried fruit extract of *T. chebula* in Balb/c strain mice. The extract at a dose of 100, 200 and 400 mg/kg proved marked neuroprotective activity [70].

Tinospora cordifolia

Tinospora cordifolia is also known as Amrita balli (Kannada), Guduchi(Sanskrit), Indian

Table 1. List of plants with potent neuroprotective activity

Sl no	Plant name	Plant parts used	Extract	Method/Models	References
01	*Abrus precatorius*	Leaves	Methanol	Elevated plus maze, Active avoidance paradigm	24
02	*Aegle marmelos*	Leaves	Ethanol	Morris water maze, spontaneous locomotar activity	26
		Leaves and fruits	Methanol	Elevated plus maze, Hebb William maze	27
03	*Allium sativum*	Fruits	Ethanol	Y-maze, Passive avoidance test	29
04	*Bacopa monnieri*	Aerial parts	Ethanol	Morris water maze	31
05	*Centella asiatica*	Leaves	Ethanol	Invitro models(inhibition of AchE or BchE activity)	34
06	*Celastrus paniculatus*	Seeds	Methanol	Invitro models(inhibition of AchE or BchE activity)	37
07	*Coriandrum sativum*	Leaves	Ethanol	Morris water maze	39
08	*Crocus sativus*	-	-	Y-maze, Passive avoidance test	41
09	*Curcuma longa*	Rhizome	Aqueous	Morris water maze, Step-through passive avoidance test	43
10	*Eclipta prostrata*	Whole plant	Ethanol	Passive avoidance task, Y-maze, Morris water maze Spontaneous locomotor activity in the open-field test	45
11	*Enhydra fluctuans*	Stems and Leaves	Chloroform	Invitro models(inhibition of AchE or BchE activity	47
12	*Ferula asafoetida*	Gum	Aqueous	Elevated plus maze, Two compartment passive avoidance test	49
13	*Ginkgo biloba*	-	-	Morris water maze,	51
14	*Glycyrrhiza glabra*	Root	Aqueous	Elevated plus maze, Hebb-william maze, Morris water maze	53
15	*Huperiza serrata*	Whole plant	Ethanol	Y-maze, Passive avoidance test	56
16	*Hypericum perforatum*	-	Methanol	Morris water maze, Open field test	58
17	*Morus alba*	root bark, leaves, branches and fruits	Methanol	Invitro models(inhibition of AchE or BchE activity	60
18	*Nigella sativa*	Seeds	Ethanol	Morris water maze	62
19	*Ocimum sanctum*	Leaves	Methanol	Open field test, Elevated plus maze, Porsolt's swim test, Learned helplessness test, Morris water maze	64
20	*Ricinus communis*	-	-	SH-SY5Y cell line studies	66
21	*Semecarpus anacardium*	Nuts	Milk	Elevated plus maze, Passive avoidance test, Scopolamine induced amnesia, Diaxepam induced amnesia, electroshock induced amnesia	68
22	*Terminalia chebula*	Dried fruit	Ethanol	Active avoidance test	70
23	*Tinospora cordifolia*	Whole plant	Methanol and aqueous	Hebb William maze, Passive avoidance test	72
24	*Valeriana wallichii*	Rhizome	Ethanol	Elevated plus maze	74
25	*Withania somnifera*	Root	Ethanol	Y-maze, Morris water maze	76

tinospora/gulancha(English) belongs to the family Menispermaceae. *T.cordifolia* is the most effective treatment for upper respiratory tract infections in children.The aqueous extract of *T.cordifolia* drastically reduced serum cholesterol and increased HDL cholesterol levels to a healthy values. Apart from this it possess many pharmacological properties like hepatoprotective, anti-neoplastic, anti-hyperglycemic, antioxidant, anti-inflammatory, antipyretic, immunomodulatory and many more [71].

Agarwal A et al. investigated neuroprotective activity of methanolic and aqueous whole plant extract of *T. cordifolia* against cyclosporine induced memory deficit in rats. The extract at a dose of 100 and 200 mg/kg proved marked neuroprotective activity [72].

Valeriana wallichii

Valeriana wallichii is commonly known as Indian valerian belongs to the family Valerianaceae. The plant's root is particularly aromatic. The herb of this plant is used to treat snake bites, hysteria, insomnia, nervous problems and also used as an analgesic. Apart from this it possess many pharmacological properties like antispasmodic, antimicrobial, anti-inflammatory, cryoprotective, anthelmintic, radioprotective andmany more [73].

Pathan A et al. investigated neuroprotective activity of ethanolic rhizome extract of *V. wallichii* against scopolamine induced learning and memory impairement in male wistar rats. The extract at a dose of 25 mg/kg proved marked neuroprotective activity [74].

Withania somnifera

Withania somnifera is commonly known as Ashwagandha belongs to the family Solanaceae. *W. somnifera* is well known medicinal plant in Ayurveda to promote physical and mental health and is used to treat almost all disorders that affect human health. It has numerous pharmacological properties like anti-inflammatory, anticancer, immunomodulatory, anxiolytic, neuroprotective, antibacterial, hypolipidemic, CVS related activites, hypolipidemic and many more [75].

Birla H et al. investigated neuroprotective activity of ethanolic root extract of *W. somnifera* against Bisphenol A (BPA) induced cognitive dysfunction in mice. The extract at a dose of 100 mg/kg proved marked neuroprotective activity [76].

To prevent and treat illness, the majority of India's rural and tribal communities rely extensively on herbal treatments. Due to the existence of a varied spectrum of active components, many Indian medicinal plants have pharmacological effects [77].

4. CONCLUSION

Behavioral factors promote nervous system health by placing moderate stress on neural stem cells. Ethnobotanical and ethnopharmaceutical studies and other natural active substances provide the majority of our present knowledge of CNS-active plants of cultural and traditional relevance. In this communication, we only looked at medicinal plants with neuroprotective activities and reported their impact on the irreversible action of cognitive impairment. The above-listed plants have anti-Alzheimer's activity by modulating altered cognitive impairment and inhibiting AchE or BchE activity.

ACKNOWLEDGEMENT

COMPETING INTERESTS

Authors have declared that no competing interestsexist.

REFERENCES

1   Rasool Hassan BA. Medicinal plants (importance and uses). Pharmaceut Anal Acta. 2012;3(10):2153-435.

2   Ahvazi M, Khalighi-Sigaroodi F, Charkhchiyan MM, Mojab F, Mozaffarian VA, Zakeri H. Introduction of medicinal plants species with the most traditional usage in Alamut region. Iranian journal of pharmaceutical research: IJPR. 2012;11(1):185.

3   Kamboj VP. Herbal medicine. Current Science 2000; 8(1): 35-9.

4   Naveen KL, Bhattacharjee A. Medicinal herbs as neuroprotective agents. WJPPS. 2021;10(4): 675-689.

5   Alzheimer's Association. Alzheimer's disease facts and figures. Alzheimer's & dementia. 2010 Mar 1;6(2):158-94.

6   Graeber MB, Mehraein P. Reanalysis of the first case of Alzheimer's disease. European archives of psychiatry and clinical neuroscience. 1999;249(3):S10-3.

7   Sivaraman D, Panneerselvam P, Muralidharan P. Memory and brain neurotransmitter restoring potential of hydroalcoholic extract of ipomoea aquatica forsk on amyloid beta Aβ (25-35) induced cognitive deficits in alzheimer's mice. Int J Pharmacol. 2016; 12(2):52–65.

8   DeTure MA, Dickson DW. The neuropathological diagnosis of Alzheimer's disease. Molecular neurodegeneration. 2019; 14(1):1-8.

9   Sivaraman D, Srikanth J. Discovery of novel monoamine oxidase-B inhibitors by molecular docking approach for alzheimer's and parkinson's disease Treatment. Int. J. Pharm. Sci. Rev. Res. 2016;40(1):245-50.

10 He W, Goodkind D, Kowal PR. An aging world; 2015.

11 Gupta BM, Bala A. Alzheimer's disease research in India: A scientometric analysis of publications output during 2002-11. Research in Neurology: An International Journal. 2013;0.

12 Hussien HM, Abd-Elmegied A, Ghareeb DA, Hafez HS, Ahmed HE, Abd El-moneam N. Neuroprotective effect of berberine against environmental heavy metals-induced neurotoxicity and Alzheimer's-like disease in rats. Food and chemical toxicology. 2018;111: 432-44.

13 Ji HF, Zhang HY. Multipotent natural agents to combat Alzheimer's disease. Functional spectrum and structural features 1. Acta Pharmacologica Sinica. 2008;29(2):143-51.

14 Riederer P, Danielczyk W, Grünblatt E. Monoamine oxidase-B inhibition in Alzheimer's disease. Neurotoxicology. 2004;25 (1-2):271-7.

15 Masliah E, Mallory M, Deerinck T, Deteresa R, Lamont S, Miller A, Terry RD, Carragher B, Ellisman M. Re-evaluation of the structural organization of neuritic plaques in Alzheimer's disease. Journal of Neuropathology & Experimental Neurology. 1993;52(6):619-32.

16 Iqbal K, Liu F, Gong CX, Grundke-Iqbal I. Tau in Alzheimer disease and related tauopathies. Current Alzheimer Research. 2010;7(8):656- 64.

17 Francis PT, Palmer AM, Snape M, Wilcock GK. The cholinergic hypothesis of Alzheimer's disease: a review of progress. Journal of Neurology, Neurosurgery & Psychiatry. 1999;66(2):137-47.

18 Patil P, Thakur A, Sharma A, Flora SJ. Natural products and their derivatives as multifunctional ligands against Alzheimer's disease. Drug development research. 2020;81 (2):165-83.

19 Huang WJ, Zhang XI, Chen WW. Role of oxidative stress in Alzheimer's disease. Biomedical reports. 2016;4(5):519-22.

20 Pocernich CB, Butterfield DA. Elevation of glutathione as a therapeutic strategy in Alzheimer disease. Biochimica et Biophysica Acta (BBA)-molecular basis of disease. 2012;1822(5):625-30.

21 Tönnies E, Trushina E. Oxidative Stress, Synaptic Dysfunction, and Alzheimer's Disease. J Alzheimer's Dis. 2017;57(4):1105– 21.

22 Kim SU, de Vellis J. Microglia in health and disease. Journal of neuroscience research. 2005;81(3):302-13.

23 Solanki A, Zaveri M. Pharmacognosy, phytochemistry and pharmacology of *Abrus precatorius* leaf: a review. International journal of pharmaceutical sciences review and research. 2012;13(2):71-6.

24 Choudhary GP, Jain AP. A promising cognition boosting effect of leaves of *Abrus precatorius*. Journal of Drug Delivery and Therapeutics. 2019;9(4-s):1177-82.

25 Lomate KA, Murthy K, Adak VS, Shete RV. A review on phytochemical and pharmacological values of *Aegle marmelos*. Journal of Drug Delivery and Therapeutics. 2021;11(2-S):162- 6.

26 Raheja S, Girdhar A, Kamboj A, Lather V, Pandita D. *Aegle marmelos* leaf extract ameliorates the cognitive impairment and oxidative stress induced by intracerebroventricular streptozotocin in male rats. Life sciences. 2019;221:196-203.

27 Kumar P, Krishnakanth K, Alla J. Effect of *Aegle marmelos* methanolic extracts of leaf and fruit pulp on learning and memory in albino rats. International Journal of Basic & Clinical Pharmacology, 2020; 9(3): 403-7.

28 Gudalwar BR, Nimbalwar MG, Panchale WA, Wadekar AB, Manwar JV, Bakal RL. *Allium sativum*, a potential phytopharmacological source of natural medicine for better health. GSC Advanced Research and Reviews. 2021;6(3):220-32.

29 Jeong JH, Jeong HR, Jo YN, Kim HJ, Shin JH, Heo HJ. Ameliorating effects of aged garlic extracts against Aβ-induced neurotoxicity and cognitive impairment. BMC Complementary and Alternative Medicine. 2013;13(1):1-1.

30 Jain PK, Das D, Jain P, Jain P. Pharmacognostic and pharmacological aspect of *Bacopa monnieri*: A review. rays (Fig. 2). 2016;8:9.

31 Uabundit N, Wattanathorn J, Mucimapura S, Ingkaninan K. Cognitive enhancement and neuroprotective effects of *Bacopa monnieri* in Alzheimer's disease model. Journal of ethnopharmacology. 2010;127(1):26-31.

32 Singh HK, Dhawan BN. Neuropsychop-harmacological effects of the Ayurvedic nootropic *Bacopa monniera* Linn. (Brahmi). Indian J Pharmacol 1997;29:S359-65.

33 Jamil SS, Nizami Q, Salam M. *Centella asiatica* (Linn.) Urban—a review. Natural Product Radiace. 2007;6(2):158-170.

34 Rahman MM, Sayeed MS, Haque MA, Hassan MM, Islam SA. Phytochemical screening, antioxidant, anti-Alzheimer and anti-diabetic activities of *Centella asiatica*. J Nat Prod Plant Resour. 2012;2(4):504-11.

35 Deodhar KA, Shinde NW. *Celastrus paniculatus*: Traditional uses and Ethnobotanical study. Ind J of Adv in Plant Research. 2015;2(1):18-21.

36 Bhanumathy M, Chandrasekar SB, Chandur U, Somasundaram T. Phyto-pharmacology of *Celastrus paniculatus*: an Overview. International Journal of Pharmaceutical Sciences and Drug Research. 2010;2(3):176-81.

37 Alama B, Haque E. Anti-alzheimer and antioxidant activity of *Celastrus paniculatus* seed. Iranian Journal of Pharmaceutical Sciences. 2011;7(1): 49-56.

38 Momin AH, Acharya SS, Gajjar AV. *Coriandrum sativum*-review of advances in phytopharmacology. International Journal of Pharmaceutical Sciences and Research. 2012;3(5):1233.

39 Elahdadi-Salmani M, Khorshidi M, Ozbaki J. Reversal Effect of *Coriandrum sativum* Leaves Extract on Learning and Memory Deficits Induced by Epilepsy in Male Rat. Zahedan Journal of Research in Medical Sciences. 2015;17(3).

40 Al-Snafi AE. The pharmacology of *Crocus sativus*-A review. IOSR Journal of Pharmacy. 2016;6(6):8-38.

41 Khalili M, Hamzeh F. Effects of active constituents of *Crocus sativus L.*, crocin on streptozocin-induced model of sporadic Alzheimer's disease in male rats. Iranian biomedical journal. 2010;14(1-2):59.

42 Jain S, Shrivastava S, Nayak S, Sumbhate S. Recent trends in *Curcuma longa* Linn. Pharmacognosy Reviews. 2007;1(1).

43 Lohit K, Anthony N, Pandit AA, George J, Jose M, Rao M, Xavier D. Assessment of *Curcuma longa linn*. on learning and memory in rats. International Journal of Basic & Clinical Pharmacology. 2015;4(6):1086.

44 Feng L, Zhai YY, Xu J, Yao WF, Cao YD, Cheng FF, Bao BH, Zhang L. A review on traditional uses, phytochemistry and pharmacology of *Eclipta prostrata* (L.) L. Journal of ethnopharmacology. 2019;245: 112109.

45 Jung WY, Kim H, Park HJ, Jeon SJ, Park HJ, Choi HJ, Kim NJ, Jang DS, Kim DH, Ryu JH. The ethanolic extract of the *Eclipta prostrate* L. ameliorates the cognitive impairment in mice induced by scopolamine. Journal of ethnopharmacology. 2016;190:165-73.

46 Sarma U, Borah VV, Saikia KK, Hazarika NK. *Enhydra fluctuans*: A review on its pharmacological importance as a medicinal plant and prevalence and use in North-East India. Int. J. Pharmcy Pharm. Sci. 2014;6:48-50.

47 Lopa SS, Al-Amin M, Hasan M, Ahammed M, Islam KM, Alam AH, Tanaka T, Sadik M. Phytochemical Analysis and Cholinesterase Inhibitory and Antioxidant Activities of *Enhydra fluctuans* Relevant in the Management of Alzheimer's Disease. International Journal of Food Science; 2021.

48 Amalraj A, Gopi S. Biological activities and medicinal properties of Asafoetida: A review. Journal of traditional and complementary medicine. 2017;7(3):347-59.

49 Vijayalakshmi SA, Bhat P, Chaturvedi A, Bairy KL, Kamath S. Evaluation of the effect of *Ferula asafoetida* Linn. gum extract on learning and memory in Wistar rats. Indian Journal of Pharmacology. 2012;44(1):82.

50 More MP, Motule AS, Dongare PN, Patinge PA, Jawarkar RD, Bakal RL, Manwar JV. Pharmacognosy, phytochemistry, pharmacology and clinical application of *Ginkgo biloba*. GSC Biological and Pharmaceutical Sciences. 2021;16(2):229-40.

51 Ge W, Ren C, Xing L, Guan L, Zhang C, Sun X, Wang G, Niu H, Qun S. *Ginkgo biloba* extract improves cognitive function and increases neurogenesis by reducing Aβ pathology in 5× FAD mice. American Journal of Translational Research. 2021;13(3):1471.

52 Sharma D, Namdeo P, Singh P. Phytochemistry & Pharmacological Studies of *Glycyrrhiza glabra*: A Medicinal Plant Review. Int. J. Pharm. Sci. Rev. Res. 2021;67(1):187-194.

53 Chakravarthi KK, Avadhani R. Beneficial effect of aqueous root extract of *Glycyrrhiza glabra* on learning and memory using different behavioral models: An experimental study. Journal of natural science, biology, and medicine. 2013;4(2):420.

54 Hasanein P. Glabridin as a major active isoflavan from *Glycyrrhiza glabra* (licorice) reverses learning and memory deficits in diabetic rats. Acta Physiologica Hungarica. 2011;98(2):221-30.

55 Jaswinder K, Rajmeet S, Gurinder S, Harpreet K, Jasvir K, Manpreet K, Parminder S, JaspreetK. A systematic review on *Huperzia serrata*. Int. J. Pharmac. Phytochem. Res. 2016;8(8): 1250-5.

56 Ohba T, Yoshino Y, Ishisaka M, Abe N, Tsuruma K, Shimazawa M, Oyama M, Tabira T, Hara H. Japanese *Huperzia serrata* extract and the constituent, huperzine A, ameliorate the scopolamine-induced cognitive impairment in mice. Bioscience, biotechnology, and biochemistry. 2015;79(11): 1838-44.

57 Saddiqe Z, Naeem I, Maimoona A. A review of the antibacterial activity of *Hypericum perforatum* L. Journal of ethnopharmacology. 2010;131(3):511-21.

58 Cao Z, Wang F, Xiu C, Zhang J, Li Y. *Hypericum perforatum* extract attenuates behavioral, biochemical, and neurochemical abnormalities in Aluminum chloride-induced Alzheimer's disease rats. Biomedicine & pharmacotherapy. 2017;91:931-7.

59 Devi B, Sharma N, Kumar D, Jeet K. *Morus alba* Linn: A phytopharmacological review. Int J Pharm Pharm Sci. 2013;5(2):14-8.

60 Kuk EB, Jo AR, Oh SI, Sohn HS, Seong SH, Roy A, Choi JS, Jung HA. Anti-Alzheimer's disease activity of compounds from the root bark of *Morus alba* L. Archives of pharmacal research. 2017;40(3):338-49.

61 Paarakh PM. *Nigella sativa* Linn.–A comprehensive review. IJNPR. 2010;1(4):409-429.

62 Hosseini M, Mohammadpour T, Karami R, Rajaei Z, Sadeghnia HR, Soukhtanloo M. Effects of the hydro-alcoholic extract of *Nigella sativa* on scopolamine-induced spatial memory impairment in rats and its possible mechanism. Chinese journal of integrative medicine. 2015;21(6):438-44.

63 Siva M, Shanmugam KR, Shanmugam B, Venkata SG, Ravi S, Sathyavelu RK, Mallikarjuna K. *Ocimum sanctum*: a review on the pharmacological properties. Int. J. Basic Clin. Pharmacol. 2016;5:558-65.

64 Raghavendra M, Maiti R, Kumar S, Acharya SB. Role of *Ocimum sanctum* in the experimental model of Alzheimer's disease in rats. International Journal of Green Pharmacy (IJGP). 2009;3(1).

65 Jena J, Gupta AK. *Ricinus communis* Linn: a phytopharmacological review. International Journal of Pharmacy and Pharmaceutical Sciences. 2012;4(4):25-9.

66 Lee E, Eom JE, Kim HL, Kang DH, Jun KY, Jung DS, Kwon Y. Neuroprotective effect of undecylenic acid extracted from *Ricinus communis* L. through inhibition of μ-calpain. European journal of pharmaceutical sciences. 2012;46(1-2):17-25.

67 Jain P, Sharma HP. A potential ethnomedicinal plant *Semecarpus anacardium* Linn. A review. Int J Res Pharm Chem. 2013;3(3):564-72.

68 Gouda SS et al., A Study on CNS Effects of Milk Extract of Nuts of *Semecarpus anacardium. linn*, (ANACARDIACEAE). 2007;49-63.

69 Rathinamoorthy R, Thilagavathi G. *Terminalia chebula*-review on pharmacological and biochemical studies. Int J PharmTech Res. 2014;6(1):97-116.

70 Rao SN, Palaksha MN, Satish S. The effects of ethanolic extract in dried fruits of *Terminalia chebula* on learning and memory in mice. Asian Journal of Biomedical and Pharmaceutical Sciences. 2013;3(20):59-62.

71 Spandana U, Ali SL, Nirmala T, Santhi M, Babu SS. A review on *Tinospora cordifolia*. International Journal of Current Pharmaceutical Review and Research. 2013;4(2):61-8.

72 Agarwal A, Malini S, Bairy KL, Rao MS. Effect of *Tinospora cordifolia* on learning and memory in normal and memory deficit rats. Indian Journal of Pharmacology. 2002;34(5):339-49.

73 Devi VS, Rao MG. *Valeriana wallichii*–a rich aroma root plant. World J. Pharm. Pharm. Sci. 2014;3:1516-25.

74 Pathan A, Alshahrani A. Neuroprotective Effects of *Valeriana wallichii* on Scopolamine Induced Learning and Memory Impairment in Rats. Pharmacognosy Journal. 2018;10(6s).

75 Gupta GL, Rana AC. *Withania somnifera* (Ashwagandha): a review. Pharmacognosy Reviews. 2007;1(1).

76 Birla H, Keswani C, Rai SN, Singh SS, Zahra W, Dilnashin H, Rathore AS, Singh SP. Neuroprotective effects of *Withania somnifera* in BPA induced-cognitive dysfunction and oxidative stress in mice. Behavioral and Brain Functions. 2019;15(1):9.

77 Prajwal S, Afrid S, Nischith S, Kumar MR. Phytochemistry, ethnopharmacology and traditional uses of *Alhagi maurorum*: An Updated Review. Asian Journal of Plant and Soil Sciences. 2021;20:221 -32.

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