Uttar Pradesh Journal of Zoology

Volume 45, Issue 1, Page 56-70, 2024; Article no.UPJOZ.3150
ISSN: 0256-971X (P)

Importance of Zebrafish as a Non-Mammalian Vertebrate Model for Studying Neurodegenerative Disorders Using Ayurvedic Medicinal Plants: A Review

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Authors' contributions

This work was carried out in collaboration among all authors. The author SP designed the study and wrote the first draft of the manuscript. The authors AM and RG analyzed and interpreted the data, Author SP managed the literature survey. Author RG has made substantial contributions to the final checking of the manuscript. All authors read and approved the final manuscript.

Article Information

DOI: 10.56557/UPJOZ/2024/v45i13855

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://prh.mbimph.com/review-history/3150

Review Article

Received: 07/11/2023
Accepted: 12/01/2024
Published: 16/01/2024

ABSTRACT

Alzheimer's disease and Parkinson's disease are debilitating neurodegenerative disorders that impose a significant burden on the affected individuals and the society as a whole. Despite extensive research efforts, effective treatments for these diseases remain elusive till date.

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Ayurveda, a traditional system of medicinal practice which originated in ancient India, has long touted the potential of various plants possessing neuroprotective properties. The effects of a few relevant Ayurvedic plants viz. Guduchi, Kapikachhu, Shankhapushpi, Turmeric, Mandukparni, Ashwagadha, Brahmi, Jatamansi etc. on several non-human primates and rodents have been reported. The therapeutic potential of those plants to mitigate the pathological hallmarks associated with Alzheimer's disease and Parkinson's disease was assessed. We have outlined the most recent research on Ayurveda's effects on neurodegenerative brain illnesses in this review article, with an emphasis on Alzheimer's disease and Parkinson's disease. As the zebrafish (*Danio rerio* Hamilton) has emerged as a useful, non-mammalian vertebrate model organism for studying a wide range of diseases, the effect of few other medicinal plants on zebrafish was also mentioned. Powerful live imaging and genetic tools which is currently available for zebrafish has transformed this fish to a top model in biomedical research and toxicity testing. However, further research is needed to elucidate the precise mechanisms of action and to translate these promising results into clinical applications. The exploration of traditional medicinal systems, in conjunction with modern scientific methodologies using novel model organisms, such as zebrafish offers a valuable avenue for the development of innovative treatments for neurodegenerative disorders.

Keywords: Ayurvedic plants; traditional medicine; Alzheimer's disease; Parkinson's disease; Zebrafish.

1. INTRODUCTION

“Alzheimer’s disease (AD) is an idiopathic and progressive brain disorder that causes a gradual decline in memory, learning and thinking skills, and eventually to carry out the simplest tasks. It usually begins after age 60, although it is possible for younger people to develop this disease. Current statistics show that over six million Americans aged 65 and above are living with AD, with a projection of about 13.8 million by 2060, and death cases have increased by 16% during the COVID-19 pandemic” [1]. “AD is an irreversible brain disorder and the most common cause of dementia. There is no cure for this disease, but certain medications and therapies can be useful to manage symptoms. The disease is named after Dr. Alois Alzheimer, a German doctor who, in 1906, noticed changes in the brain tissue of a woman who died of an unusual mental illness. He found clumps of starch like materials, known as amyloid plaques and tangled bundle of fibres, known as neurofibrillary tangles, in her brain. The progressive cognitive decline in AD is associated with the accumulation of amyloid-beta (Aβ) and tau proteins which causes death of the brain cells” [2]. The human brain contains more than 100 billion neurons and other glial cells which synchronously work to control thought, memory and language. Scientists believe that these amyloid proteins forming plaques and twisted tau protein fibres block the communication between neurons which prevent them from carrying out their processes. In addition to nerve cells, neuroglial cells especially the astrocytes also play a major role in the progression of this disease. The slow and ongoing death of the neurons results in the symptoms of Alzheimer’s disease. Nerve cell death starts in one area called hippocampus, which controls memory and then spreads to other areas gradually. In latter stage of this disease, people experience sun downing and become anxious or aggressive and may wander away from home. Patients become more demanding, restless, upset, suspicious or disoriented and they may hallucinate at night. Sun downing results from a lack of light, which fails to stimulate certain areas of brain, exacerbating the manifestations of dementia. Although there is no cure for AD, some selected medicines may help control behavioral symptoms such as sleeplessness, agitation, wandering, anxiety and depression.

“On the other hand, with ageing and increasing life span of the world population, age related problems like Parkinson's disease (PD) are receiving growing attention from the scientific fraternity. Among the neurological disorders, this disease is the fastest growing in worldwide” [3]. “PD is a chronic nervous disease which is characterized by a fine, slowly spreading tremor, bradykinesia, muscular weakness and rigidity and a peculiar gait. Persons with Parkinson's disease have diminished levels of dopamine, a neurotransmitter, in their brains, which causes them to exhibit signs of a fine tremor of the hands or feet that spreads slowly to other parts of the body” [4-6]. “In advanced cases of Parkinson's, individuals have an expressionless face and speech impairment. In addition, they

have a bowed head, a forward bend to their body, and thumbs that are turned in toward their palms. PD causes flexed arms as the muscles become rigid. An examination may show jerky, stiff movements, known as cogwheel rigidity and difficulty initiating or completing voluntary movements. As per the estimate coming out from the Global Burden of Disease Study, the number of PD case will double from about 7 million in 2015 to about 13 million in 2040, suggesting for a potential PD Pandemic" [7]. "While this extrapolation based on future growth of population is just an estimate, it highlights the enormous burden that PD and related neurodegenerative conditions can pose for society. Till date, treatments address only the symptoms but they fail to stop the progression of the disease and PD patients continue to experience a higher mortality rate compared to the general population" [8].

2. IMPORTANCE OF AYURVEDIC PLANTS

"Traditional remedies could be adjunct therapeutic options to allay wide-ranging pathological cascades of AD. Medicinal herbs and plants provide several options to modify the progress and symptoms of AD. Currently, there is a growing impetus in the preparation and production of novel drugs based on medicinal plant products and their scientific as well as the commercial significance seems to be gathering momentum in various health-relevant areas. These plant-derived products undergo a very stringent and careful process of standardization and subsequently their efficacy and safety are further analyzed before any specific case of application" [9-13]. "Ayurveda offers a holistic approach of treatment along with a list of nootropic herbs and phytochemical studies have shown the presence of many valuable compounds and formulations such as lignans, flavonoids, tannins, polyphenols, triterpenes, sterols and alkaloids. These components essentially exhibit a wide spectrum of important pharmacological activities including neuroprotective, anti-inflammatory and immunomodulatory effects which modulate neuroendocrine and immune activities, enhance memory, intellect, rejuvenate brain functions and improve quality of life" [11-15]. "Several scientific studies have till date described the use of various Ayurvedic medicinal plants and plant- derived components, which have significantly strengthened the functional activity of the nervous system and helped to restore memory" [16]. A strong knowledge base of traditional systems coupled with contemporary science may provide new functional leads for age-associated neurodegenerative disorders at preventive and curative levels and evolution of new drug therapies and development processes, though further research is needed. We have outlined the most recent research on Ayurveda's effects on neurodegenerative brain illnesses in this review article, with an emphasis on AD and PD. Additionally, we have made an effort to comprehend the plants that have the most potential effectiveness and that might be used in future clinical studies.

3. ROLE OF AYURVEDIC PLANTS IN NEURODEGENERATIVE DISEASES WITH MAJOR FOCUS ON AD AND PD

The most significant Ayurvedic therapeutic plants, their components, and their effects on AD and PD are discussed. The useful role of few other Ayurvedic herbs in brain diseases or disorders has been summarized in Table 1.

3.1 Guduchi (*Tinospora cordifolia*)

Tinospora cordifolia, commonly named as Guduchi is an herbaceous vine belonging to the family Menispermaceae and is an important medicinal plant in Ayurveda for treating various ailments (Fig. 1). "It is a widely distributed and essential Ayurvedic plant in the Indian subcontinent which has been traditionally used as an anti-diabetic agent and regulates bile secretion, reduce burning sensation and treat several urinary tract infections" [17]. "The shrub contains various classes of compounds such as alkaloids, glycosides, aliphatic compounds, polyphenols, lactones, steroids and terpenoids. It has been reported to possess protective effects against Alzheimer's disease and other neurodegenerative diseases. In clinical studies, *T. cordifolia* is applied either in the form of a polyherbal formulation or alone for general amendment of the memory function" [18]. "*T. cordifolia* is one of the most important herbs in Ayurveda and has remarkable effects in memory impairment and learning enhancement" [19]. "Only a few preclinical studies have tested *T. cordifolia* for its neuroprotective benefits and mechanisms have not been clearly defined. Administration of 50% ethanolic extract of *T. cordifolia* (140 mg/kg, orally) for 15 days in sleep-deprived rats resulted in significant improvement of cognitive functions (e.g., novel object recognition) compared to vehicle-treated sleep-

deprived animals" [20]. "In a rat model of drug (scopolamine)-induced amnesia, a combination of ethanolic extract of *Tinospora cordifolia*, *Bacopa monnieri*and *Evolvulusalsinoides* (200 mg/kg; administered orally) was reported to provide significantly greater nootropic effects than any of the herbs while used alone or in combinations of any two" [21]. "In primary cerebellar neuronal cultures exposed to neurotoxic insult (monosodium glutamate), pre-treatment with butanol extract of *T. cordifolia*was found to normalize the stress-induced down regulation in the expression of neuronal markers (MAP-2, GAP-43, NF200) and an anti-apoptotic marker (Bcl-xL)" [22]. "The role of *T. cordifolia* in cholinergic mechanisms needs to be clearly understood and the outcome can lead to have positive impact to AD patients" [18].

3.2 Kapikachhu (*Mucuna pruriens*)

Mucuna pruriens (also known as 'the cowhage' or 'velvet' bean; and 'atmagupta' in India) is a climbing legume endemic in India and in other parts of the tropics including Central and South America (Fig. 1). Ayurvedic texts described Kampavata, a nervous malady bearing similarities to Parkinson's syndrome, responding to atmagupta (mucuna) [23] and mucuna seed preparations are in contemporary use for the treatment of PD in India [24]. "Levodopa (L-dopa) was first isolated from the seeds of *M. pruriens* in 1973 and when the value of L-dopa for the treatment of PD was known, scientific interest in plants rich in L-dopa was revived. In a study, The MPTP-induced neurotoxicity was significantly alleviated by a *Mucuna pruriens* extract treatment containing L-DOPA and a mixture of rich novel phytochemicals through the NF-kB and pAkt pathways. The results showed that MP extract may have resulted in reduction of MPTP-induced neuro-inflammation, restoration of biochemical and behavioral abnormalities in PD mice, and thus ultimately established a theoretical foundation for its traditional use" [25]. "The long-term antiparkinsonian effects of a parenterally administered water extract of *M. pruriens* seed powder was also reported to pave the way for new drug discoveries and treatment strategies for PD" [26]. "*M. pruriens* seeds extract (MPE) of 40 g/mL resulted in reduction of the precipitation of innate negative geotaxis activity in *Drosophila melanogaster* by 35.3 % and 32.8 % respectively, when dopaminergic neurotoxins (6-OHDA and rotenone) were used. MPE, in addition to L-dopa, produced bioactive compounds that may have neuroprotective properties against PD" [27]. "The further study suggested that tolerability might be better with mucuna than with standard L-dopa preparations" [28]. However, no published randomised, controlled studies have yet provided evidence of the efficacy of mucuna extracts in the treatment of PD.

Table 1. Roles of few Ayurvedic plants against some neurological diseases

Ayurvedic plants	Scientific name	Major roles
Adraka	*Zingiber officinale*	Improves recall and retention [86].
Amalaki	*Emblica officinalis*	Antioxidant, improves amnesia and memory deficits [87].
Jatiphala	*Myristica fragrans*	Improves learning and memory deficits [88].
Dhanyaka	*Coriandrum sativum*	Antioxidant, anti-inflammatory activity [89].
Kushmanda	*Benincasa hispida*	Neuroprotective, antioxidant, Nootropic activity [90].
Shatavari	*Asparagus racemosus*	Antioxidant, Inhibiting MAO-A and MAO-B [89].
Aparajita	*Clitoria ternatea*	Increases levels of ACh, Nootropic effect [91].
Sarpagandha	*Rauvolfia serpentina*	Hypertension, Insomnia, Depression [92].
Tulsi	*Ocimum sanctum*	Acetyl choline inhibition [93,94].
Neem	*Azadirachta indica*	Improvement of cognition [94].
Bringraj	*Eclipta alba*	Antioxidant, Improves learning [95].
Kesar	*Crocus sativus*	Antioxidant property, Inhibits impairment of hippocampal synaptic plasticity and fibrillogenesis [89,96].
Almond	*Prunus amygdalus*	Destabilizes the Amyloid-β Fibrils [97].
Garlic	*Allium sativum*	Down regulation of Amyloid-β Induced apoptosis in PC12 cells [98].

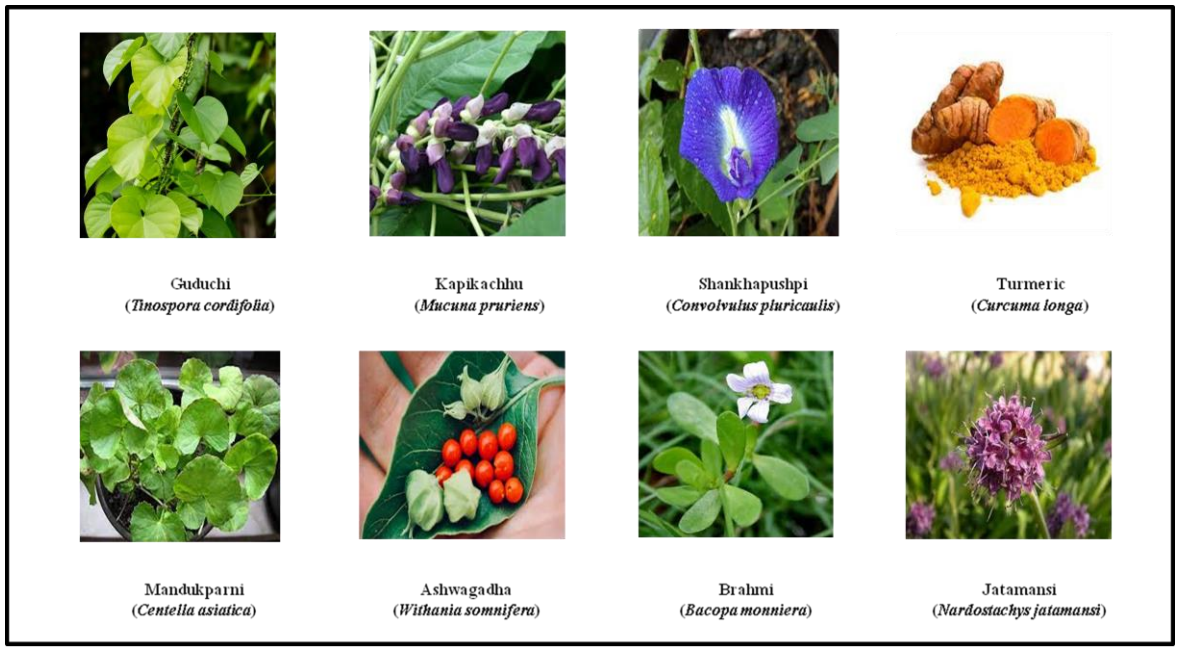

Fig. 1. Selected Ayurvedic plants with potential role against AD and PD

3.3 Shankhapushpi (*Convolvulus pluricaulis*)

"Convolvulus pluricaulis is an herb found in India and Burma which is used in Ayurveda" [29]. Shankhpushpi has been used traditionally as a brain tonic and is believed to play a potentially effective role in a wide range of issues by demonstrating anxiolytic, relaxant and anti-obsessive effects as well as nootropic effects (Fig. 1). "This plethora of medicinal properties attributed to *C. pluricaulis* has been credited to its numerous phytoconstituents, which are primarily alkaloids, flavonoids, coumarins, and polyphenols. This plant contains an alkaloid, namely, Shankhpuspine, which is known as a chemotaxonomic marker for this species" [30]. "A wide range of secondary metabolites, including triterpenoids, flavonol glycosides, anthocyanins, andsteroids, has been isolated and may be responsible for Shankhpushpi's nootropic and memory-enhancing properties. In addition to other pharmacological activities, a dose-dependent enhancement of memory was observed in mice that were administered extracts of CP" [31]. "*C. pluricaulis* possesses several neuro-pharmacological properties including anti-inflammatory, anti-oxidant, anti-convulsant activities. It has been reported to be extremely beneficial for nervous disorders such as stress, anxiety, mental fatigue and insomnia" [32]. "The ethanolic extract of *C. pluricaulis* and its ethyl acetate and aqueous fractions was reported to result in significant improvement of learning and memory in rats" [33]. "Further, administration of *C. pluricaulis* extracts for 7 days was found to enhance memory in aged mice as Hippocampal regions associated with the learning and memory functions showed a dose-dependent increase in acetylcholine esterase activity in the CA1 and CA3 area after undergoing treatment with *C. pluricaulis"* [34]. "In another study, young and adult rats incubated with aqueous root extract of *C. pluricaulis* showed a significant increase in passive avoidance learning and retention" [115]. "A significant increase in dendritic intersections, branching points and dendritic processes arising from the soma of neurons in the amygdale region in *C.pluricaulis* -treated rats was also observed in comparison with age-matched saline controls, suggesting that this plant enhances memory by increasing the functional growth of neurons" [35].

3.4 Turmeric (*Curcuma longa*)

"Turmeric is a rhizomatous herbaceous perennial plant of the ginger family, Zingiberaceae (Fig. 1). The active constituents are thought to be turmerone oil and water soluble curcuminoids, including curcumin" [36]. "Curcumin is the principal curcuminoid and is responsible for the yellow colour of the turmeric root" [37]. "The anti-inflammatory, antiseptic and antibacterial properties have long been utilized in the Indian system of medicine to treat a variety of disease conditions. Several studies have already proved

that this compound has a potential role to treat Alzheimer's and Parkinson diseases" [38]. "A study has recently proved that it can reduce the plaque depositions (by crossing the blood–brain barrier in Tg 2576 mice as well as the amyloid plaque burden) and even decrease the oxidative damages which further exhibits its beneficial role against AD" [39]. "Curcumin pharmacology provides us insights into its medicinal potential in the treatment of neurodegenerative disorders such as Alzheimer's disease and Parkinson's disease, as well as for other brain malignancies" [40]. "Some findings reflected the potential of curcumin in neurodegenerative brain diseases as prevention and treatment agent" [41]. "In various central nervous system (CNS) disorders like Parkinson's disease, Huntington disease, Alzheimer's syndrome, the curcumin nanoparticles and their potential mechanism(s) of action have been clarified" [42]. "Epidemiologic studies exhibited a 4.4-fold lower incidence of AD in the Southeast Asian countries where turmeric is commonly used as a dietary spice" [43]. "Other studies indicated that the non-steroidal anti-inflammatory property of turmeric is associated with a reduced risk of AD" [44]. "It was reported to reduce oxidative damage and reversed the amyloid pathology in an AD transgenic mouse" [45,46]. "Direct injection of curcumin into the brains of the mice with AD not only hampered further development of plaque but also reduced the plaque levels" [46]. "Low dose of this compound further reduced the cytokines level of IL-1β" [39]. "In another study, Curcumin administration increased hippocampal neurogenesis in chronically stressed rats, similar to classic antidepressant imipramine treatment" [47]. "As a result of these promising findings in animal models, clinical trials of oral curcumin supplementation in patients with early AD are already under way" [48]. "Longvida, an item for consumption of Curcumin is now in phase II clinical trials and has been approved by FDA against AD" [49]. "However, larger and controlled trials are necessary to ascertain the efficacy of oral curcumin supplementation in AD" [50].

3.5 Mandukparni or Gotu kola (*Centella asiatica*)

Commonly known as Mandukparni or Gotu kola or Indian pennywort or jalbrahmi, it has been used as a medicine in the Ayurvedic tradition of India for thousands of years and listed in the historic 'Sushruta Samhita', an ancient Indian medical text [51,52]. In the Ayurvedic system of medicine, it is one of the most important rejuvenating herbs for nerve and brain cells and is believed to be capable of increasing the level of intelligence, longevity, and memory [53,54]. *C. asiatica* has been used as a neuroprotective agent in traditional Indian medicine, and is promising in the treatment of inflammatory disorders, wound healing and immunomodulatory action (Fig. 1). The herb extracts have a neuroprotective function due to the inhibition of AChE development and improved visual memory development [55]. Asiaticoside derivatives, including Asiatic acid (AA) and Asiaticoside, were shown to reduce hydrogen peroxide-induced cell death, decrease free radical concentrations, and inhibit beta-amyloid cell death *in vitro*, suggesting a possible role for Gotu kola in the treatment and prevention of AD and beta-amyloid toxicity [56]. *C. asiatica* water extract (CAW) and some of the compounds present in it have been reported to increase dendritic arborization and synaptic differentiation, which exhibits its cognitive benefits. Furthermore, CAW and its constituent compounds strengthened these endpoints in neurons. Hence these findings indicate that the extract has therapeutic potential even beyond Alzheimer's disease [57].

3.6 Ashwagadha (*Withania somnifera*)

Ashwagandha is a member of the Solanaceae family, and the root is the part that is widely used (Fig. 1). In Ayurveda, this herb is best known for usage as a nerve tonic, aphrodisiac, and 'adaptogen' and helps the body to control the stress and produce relaxation [58,59]. Active compounds found are Withanolide A, Withanolide B, Withanolide Q, Withanoside IV, Withanoside V, Ashwagandhanolide, sominone, Withanone, Withaferin A, Sitoindoside IX andSitoindoside X [60,61]. A subset of these components (withanamides) has been shown to scavenge free radicals generated during the initiation and progression of AD. Neuronal cell death triggered by amyloid plaques was also blocked by withanamides [62,63]. Molecular modeling studies showed that withanamides A and C uniquely bind to the active motif of beta-amyloid (Aβ 25-35) and prevent fibril formation [63,64]. Aqueous extracts of this herb have been found to increase cholinergic activity, including increase in the acetylcholine content and cholineacetyl transferase activity in rats and this might be the basis of the cognition-enhancing and memory-improving effects [65,66]. It is also found to increase memory by creating good impact on cholinergic signaling [67,68]. It further helps in regenerations of axons and dendrites

also and even protect nerve cells from cell death [67,68]. Some of the earlier experiments which were carried out on mice models like in j20 mice support the usage of this plant as anti-AD agents [67]. Others experiments suggest that its active compounds are helpful in reducing the fibril formation and reducing the toxicity of proteins Aβ [60,69]. Additionally, one pilot study has revealed that *W. somnifera* (L.) root extract has ameliorated deficits in cognition and memory loss in adults with mild cognitive impairment [60]. In *Drosophila,* it was found to reduce ROS, improve cholinergic functions, attenuate the apoptotic cues and down-regulate inducible nitric oxide synthase (iNOS) in dopaminergic neurons [60]. Moreover, root extract of this plant has led to up-regulate tyrosine hydroxylase activity and protected dopaminergic neurons. Although the data mentioned above are quite promising for the use of Ashwagand haas an anti-AD agent, additional clinical trials need to be conducted to support its therapeutic use.

3.7 Brahmi (*Bacopa monniera*)

Brahmi (also known as Bacopa) is a bitter-tasting creeper plant found in damp and marshy areas (Fig. 1) and is traditionally used in Ayurvedic medicine as a nerve tonic, diuretic and cardiotonic agent and also a therapeutic agent against epilepsy, insomnia, asthma and rheumatism [70]. Traditionally, *B. monniera* was used to improve memory and cognitive function [71]. The extract of this plantis also very well known for functioning against several brain diseases like AD and PD and it has been investigated extensively for their neuropharmacological effects and their nootropic actions [72]. The main compounds that are founds in extracts are bacoside A, bacoside B, bacopasaponins, D-mannitol, acid A, herpestine, hydrocotylineasiaticoside, thanakunicidebetulinic acid, betulic acid, wogonin, oroxindin, stigmastarol, β-sitosteroljujubacogenin, pseudo-jujubacogeninbrahmic acid, brahamoside, brahminoside and iso-brahmic acid [73,74]. Recent researches working on AD have reported important roles of Brahmi. It has shown to improve memory performance and gain of cognitive functions which are essentially the signs of AD recovery. *B. monniera* was also found to inhibit cholinergic degeneration and displayed a cognition-enhancing effect in a rat model of AD [75]. A team of researchers also reported that a standardized extract of this plant performed the effects such as (i) depletion of acetylcholine, (ii) reduction in choline acetyltransferase activity and (iii) decrease in muscarinic cholinergic receptor binding in the frontal cortex and hippocampus [76]. It was also reported that Brain-derived neurotrophic factor (BDNF) is related with neuronal plasticity and memory [77]. On the other hand, Glial fibrillary acidic protein (GFAP) which is known to regulate the morphology of astrocytes, interactions between neuroglia and memory forming mechanisms were increased due to administration of extracts in mice model [78,79]. In a study on PSAPP mice where Brahmi extract was used experimentally, proteins levels of Aβ40 and Aβ42 were decreased in brain by approximately 60% [78] where deposition of Aβ protein acts as the key factor of neurodegeneration causing AD. An enriched phytochemical composition of this plant was evaluated for short-term safety and tolerance in healthy adult volunteers. A detailed examination [80] of clinical, haematological, biochemical, and electrocardiographic parameters did not reveal any untoward effects in any of the volunteers who received oral administration of a single capsule containing the enriched herb for 30 days (300 mg for the first 15 days and 450 mg for the next15 days). On the basis of the above-mentioned studies and other clinical investigations carried out to establish the efficacy of *B. monniera* in memory and attention disorders, this herb has now been introduced in the Indian market for treatment of memory and attention deficit disorders [81,82]. These clinical studies with *Bacopa* serve as a model for the way forward for other herbs to ascertain their effective dosage range, the time required to attain therapeutic levels and their effects over a longer term of administration.

3.8 Jatamansi (*Nardostachys jatamansi*)

Nardostachys jatamansi(Family: Caprifoliaceae Juss.), popularly known as Indian spikenard, is a critically endangered medicinal plant which grows at high altitudes in the alpine and sub-alpine regions of the Himalayas (Fig. 1). Its medicinal properties are well established in traditional medicines including Ayurveda. The roots and rhizomes of this plant have great medicinal values. The bioactive compounds present in this plant are sesquiterpenoids, valerianan oids [83]. An alcoholic extract of this plant administered to both young and aged mice significantly improved learning and memory and reversed the amnesia along with powerful anti-oxidant activity [84]. Thus, its potential to decrease the memory deficit and insomnia could

be taken advantage of especially against AD. It is also experimentally proved that 92% patients of PD on Herbal composite had grade I clinical retrieval and better excellence of life rather than conventional therapy. It also played significant role to check degeneration of neural cells in substantia nigra [85]. Still, robust clinical validation needs to be performed for its general medical use.

4. CRITERIA OF SELECTING ANIMAL MODELS FOR THE STUDY OF PD AND AD

"A suitable animal model for neurodegenerative diseases like AD and PD should essentially exhibit histopathologically characterizable progressive loss of dopamine neurons together with other neurons and significant reduction in dopamine level. Moreover, the onset of the disease should be in adulthood this should manifest in such a way that it would mimic the PD-affected human motor symptom such as bradykinesia, rigidity, postural instability, and resting tremor, with motor features being responsive to L-DOPA or any anti-PD drug therapy. Even though non-human primate and mouse has been the traditional model of AD and PD, low cost of maintenance, shorter life cycle and defined neuropathological profile is making zebrafish an emerging and more interesting model for the study of AD and PD" [99].

5. ADVANTAGES OF USING ZEBRAFISH MODEL

"In biological research, several small fish species are gaining increased popularity as model organisms for developmental, physiological, and biomedical research. Particularly prominent among these has been the zebrafish (*Danio rerio*), a small cyprinid teleost, which offers researchers the attractive combination of various features viz. Genetic tractability, rapid *ex vivo* development, optical transparency, completed genome sequencing and annotation project and a rapidly expanding resource of genetic and biochemical reagents including numerous mutant and transgenic lines which makes it a significantly powerful system for disease modeling and drug screening" [100]. Other advantages of zebrafish models include neuro-morphological similarity to humans, easy maintenance, high fecundity [101] and the availability of well-established behavioral assays [102]. "Zebrafish are also sensitive to all major classes of CNS drugs and they serve as a cost-effective model organism for in vivo drug screening and also show high potential for high-throughput screening" [103]. Mounting evidence further supports the utility of zebrafish in studying CNS effects of Ayurvedic plants (Table 2).

"The effect of *Centella asiatica* (CA) a known neurotonic was studied to Brain-derived Neurotrophic Factor (BDNF) as a neuroprotectant and apoptosis as hallmark of PD in rotenone-induced zebrafish (*Danio rerio*) was investigated in a study" [104]. "Also, zebrafish motility and dopamine (DA) level in the brain was studied. The results suggested that methanolic extract of CA could protect Parkinsonian syndrome conserved dopaminergic neuron through increasing BDNF as neurotrophic factor" [104]. "In another study the neuroprotective potential of *Withania somnifera* leaf extract (WSLE) was evaluated following exposure to waterborne B[a]P. Wild-type zebrafish (*Danio rerio*) were designated as naive, control (dimethyl sulfoxide), WSLE, B[a]P, and B[a]P + WSLE groups" [105]. "Behavioral studies showed reversal in scototaxis (anxiety-like) behavior in B[a]P group and was restored by WSLE co-supplementation in B[a]P + WSLE group. The study showed that the reversal in scototaxis behavior following exposure to waterborne B[a]P might be associated with neuromorphological alterations in PGZ, whereas a pioneer ethnopharmacological approach of WSLE cosupplementation showed its neuroprotective role to restore normal scototaxis of zebrafish" [105]. "In a recent study, the effect of *Ocimum sanctum* leaves aqueous extract on the memory impairment and memory enhancing activity in zebrafish was studied using rivastigmine as the standard drug and scopolamine as the memory impairing agent" [106]. "The results of the study contribute to the ability of this leaf extract in ameliorating the memory impairment effects of scopolamine and further indicated that it could be used as a potential drug for neurodenegerative diseases like AD" [106]. In another investigation, it was targeted to evaluate the chemical composition, as well as the cognitive-enhancing, anxiolytic, and antioxidant activities of the aqueous extract from *Ceratonia siliqua* (CsAE) leaves against 6-hydroxydopamine (6-OHDA) zebrafish Parkinson's disease (PD) model [107]. Qualitative and quantitative analyses were performed by the ultra-high-performance liquid chromatography (UHPLC) analysis. The memory performance was evaluated through the NTT and Y-maze tests. Additionally,

Table 2. Selected study of Ayurvedic plants against brain disorders usingzebrafish model

Ayurvedic plants	Effect on neurological disorders
Indian pennywort	Protected dopaminergic neurons from rotenone toxicity by increasing BDNF levels and reduced α-synuclein aggregation [104].
Indian ginseng	Improved brain antioxidant status and neuroprotection against benzo[a] pyrene toxicity [105].
Tulsi	Protected memory against scopolamine [106].
Carob	Antioxidant and anti-AChE activity, improved cognitive function in the 6-OHDA-induced PD model [107].
Asian pigeonwing	Reduced stress responses induced by reserpine [108].

the *in vitro* and *in vivo* antioxidant status and acetylcholinesterase (AChE) activity were also assessed. The overall findings demonstrated that CsAE presented positive antioxidant and anti-AChE activities, which contributed to the improvement of cognitive function in the 6-OHDA zebrafish PD model [107]. The metabolite profiles of crude *Clitorea ternatea* root extract (CTRE), ethyl acetate (EA) and 50% aqueous methanol (50% MeOH) fractions were investigated using ultrahigh-performance liquid chromatography-diode array detector-tandem mass spectrometry (UHPLC-DAD-MS/MS), while their effect on the stress-like behavior of zebrafish, pharmacologically induced with reserpine, was investigated [108]. The results of the study provided further evidence that the basis for the use of *C. ternatea* roots in traditional medicine to alleviate brain-related conditions, such as stress and depression, is attributable to the presence of clitorienolactones and the isoflavonoidal constituents [108].

6. CHALLENGES OF USING ZEBRAFISH MODEL

A few Ayurvedic plants have till now been tested for neurological research using zebrafish models, resulting in a lack of critical mass of empirical evidence in the field. The use of Ayurvedic plants extract in different sexes, strains and ages of zebrafish is also a challenge since the response could be different to various anxiolytic compounds and drugs that might be affecting their general locomotor activity often unsuitable model organisms for drug discovery and failure to use individual ('personalized') medicine-based approaches [109,110]. there are also some challenges and limitations in this field, including problematic unavailability of standards for raw materials, identification of bioactive compounds and pharmacognostic analyses, low bioequivalence and safety concerns. The dose standardization for bioactive molecules from Ayurvedic plants is also an important, yet often neglected consideration, especially since animal doses often differ from traditional doses recommended clinically [111].

7. CONCLUSION

This review suggests that many of the Ayurvedic medicinal plants listed here, have a highly promising and potential effect to cope with neurodegenerative brain diseases like AD and PD. We have also summarized that among all the Ayurvedic medicinal plants few important herbs have greater effect on the deadliest diseases like AD and PD. The problems of using novel animal models must be solved in near future by conducting thorough laboratory experiments in different model species like Zebrafish along with other established model organisms. High-throughput imaging assay can be developed for drug neurotoxicity screening, to better understand drug pharmacokinetics and pharmacodynamics necessary for large-scale Ayurveda studies. While many experiments with Ayurvedic drugs involved adult fish have been reported till date, zebrafish larvae are emerging as another promising tool [112] since their small size enables placing them into multi-well plates filled with only 200 µl of fluid, requiring only few mg of compounds for screening [113]. The availability of powerful live imaging and genetic tools along with the optimized and automated systems for drug screening has transformed the zebrafish into a valuable model organism in modern biomedical research, drug discovery and toxicity testing [114]. Studies delve into the underlying molecular mechanisms of action, revealing potential neuroinflammatory and oxidative stress-modulating pathways influenced by these plant compounds may be a new avenue to study. Positive and fruitful outcome from studies and research works in future might lead to successful clinical trials and the proposed medicinal plants could then be further used to

develop novel therapeutic approaches against neurodegenerative diseases.

ACKNOWLEDGEMENTS

We are privileged to express our sincere thanks to all the Principals of three colleges for their constant support during the preparation of this review paper.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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