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Review Article

Neuroprotective Promise of Medicinal Plants: A Systematic Study of Anti-Alzheimer's Potential

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ABSTRACT

Alzheimer's disease (AD) is characterized as a neurodegenerative disorder, commonly seen in elderly people. In India around 3.7 million elderly people are suffering from dementia and it might be raised to increase two-fold by 2030 and threefold by 2050. Recently herbal therapy of Alzheimer's is gaining the popularity & it allows the researcher to find the better plant-oriented drugs for the treatment of Alzheimer's disease as current research highlights the usefulness of herbal drugs in management of Alzheimer's disease. This review collective evidence of Anti-Alzheimer's potential of medicinal plants. Comprehensive review was done through the data collected through different scientific data bases Pub Med, Science Direct, Google Scholar, SCOPUS & google search engine. The search was done using different key words like Plants, extracts, Alzheimer's disease, Anti-Alzheimer's activity, Anti-Alzheimer's Effect. Result demonstrates extraction was performed using solvents like ethanol, methanol, aqueous, chloroform, n-Hexane. Ethanol was found to be preferred solvent in most of the investigations. Maceration method for the extraction was preferred in extraction. Different in vivo & in vitro methods employed to investigate anti-Alzheimer's activity of medicinal plants. Possible mechanism of action for the plant is found to inhibit the enzyme cholinesterase, anti-inflammatory action, antioxidant action & affecting Aβ plaques.

INTRODUCTION

Alzheimer's disease (AD) is characterized as a neurodegenerative disorder, commonly seen in elderly people[1]. The primarily hallmarks which can be seen are like neuronal loss, senile plaques and neurofibrillary tangles etc[2]. The disease spreading rate is increasing approximately 5% in age of individuals 65-74, 13.1% in age of 75-84 and 33.3% in people of age 85 or older[3]. In India

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around 3.7 million elderly people are suffering from dementia and it might be raised to increase two fold by 2030 and three fold by 2050[4].Currently in the year 2021, Asia experienced a 250.44% increase in prevalent cases, a 297.34% rise in mortality, and a 249.54% for AD and other dementias compared to 1990[5].Mainly three cases can be observed in Alzheimer's disease case A: related to genetics, case B: related to a language variant of Alzheimer's disease, Case C: related to typical amnestic variant[6]. Main identical symptoms of AD are like forgetfulness, difficulty in concentration, language difficulties, issues related to planning and problem solving, difficulty in performing previously familiar tasks, problems in social behaviour, and complexity in spatial relationships in their day to day routine[7]. Basic pathology may be seen particularly in the hippocampus, amygdala and cortical association areas of the frontal, temporal and parietal cortices, it can also associated with subcortical nuclei such as the serotonergic dorsal raphe and the cholinergic basal nucleus[8].

In macroscopic examination there is the atrophy of the hippocampus and cerebral cortex, which can be appeared in AD more sharply due to age[9]. The pathogenesis of amyloid starts with different cleavage of amyloid precursor protein (APP), which synthesize insoluble Aβ fibrils. Aβ then oligomerizes in different forms and, diffuses into synaptic clefts, and interferes with synaptic signalling in brain[10]. Inflammation plays a crucial role in the pathogenesis of AD, and the chronic inflammation in the brain, often referred to as neuro inflammation, is mainly observed in AD patients and has been leading in disease progression & neuronal damage. Intracellular aggregations contain abnormally configured, excessively phosphorylated tau protein also causes AD[11,12].

Hypothesis of AD:

The amyloid cascade hypothesis states that Alzheimer's disease is a condition which begins with abnormal cleavage of the protein i.e. amyloid precursor protein (APP), which causes leading excessive formation of amyloid-beta (Aβ)-which are especially Aβ form which are toxic in nature[13]. The tau hypothesis states that causative agents of Alzheimer's disease includes abnormalities in the tau protein, responsible for stabilization microtubules in neurons. During AD, tau abnormality causes disruption of the microtubule network, impairs cell transport, affects synapses, and damages mitochondria, leading to neurodegeneration conditions in patients[14]. The cholinergic type of hypothesis of Alzheimer's disease (AD) shows that cognitive decline is mainly occurring and it is linked to the loss of cholinergic neurons and reduced acetylcholine neurotransmission, specifically from the basal forebrain[15]. The presenilin hypothesis generally consisting of loss of PS1 function, which is not just amyloid-beta (Aβ) build up, but it also causing the neurodegeneration in Alzheimer's disease[16]. Oxidative stress type of hypothesis in Alzheimer's disease is mainly causing due to imbalance between free radicals and antioxidant defenses, rising the condition of neurodegeneration, specifically in the cortex and hippocampus[17].

Treatment of AD:

Certain drugs like Donepezil, belongs to a selective cholinesterase inhibitor, which beneficial for some patients of AD in case of symptomatic treatment ranging from mild-to-moderate Alzheimer disease. Currently one third of AD patients are continuing to take donepezil 5mg and showing clinical improvement after everything 6 months of therapy[18]. Memantine is another drug which is used to treat moderate to severe Alzheimer's disease. This drug basically works on

the principle of blocking a brain chemical called as glutamate at its exited state it becomes too active, which helps to protect brain cells[19]. Donanemab and Lecanemab are monoclonal antibody drug targeting N3pG (Pyroglutamate-modified amyloid-beta plaques) and novel Alzheimer's disease therapy targeting amyloid beta respectively[20]. Some other biofabrication of silver nanoparticles (AgNPs) using Erythrina variegata leaf extract are useful in treatment of Alzheimer's disease hence their antioxidant and anti-inflammatory properties, which reduces oxidative stress and neuronal damage. This extract-stabilized AgNPs may inhibit amyloid-beta aggregation, a key factor of pathological hallmark of Alzheimer's disease, hence thereby protecting neuronal functions. Also, the nanoparticles' small size and crystalline nature which results in enhancing their bioavailability and cellular uptake, increasing their therapeutic efficacy in Alzheimer's models[21].

Medicinal Plants in AD:

Drugs used currently in the Alzheimer's disease are targeting the elevation of neurotransmission in the synapse through various mechanism by inhibiting the acetyl-cholinesterase enzyme, blocking NMDA receptor or other cerebro-active agents[22,23]. The dietary supplements & antioxidants also found to have the proper antioxidant activity which may be helpful in Alzheimer's disease[22,24,25]. Recently herbal therapy of Alzheimer's is gaining the popularity & it allow the researcher to find the better plant oriented drugs for the treatment of Alzheimer's disease[26,27]. The current research highlights the usefulness of herbal drugs in management of Alzheimer's disease[28]. Some of the medicinal plants proved to have anti Alzheimer's activity are *Garcinia hanburyi*[29], *Murraya koenigi*[30], *Citrus maxima*[31], *Salvia officinalis*[32], *Piper nigrum*[33], *Echium amoenum*[34], *Rosa damascene*[35], *Streblus asper*[36].

METHODOLOGY:

Comprehensive review was done through the data collected through different scientific data bases Pub Med, Science Direct, Google Scholar, SCOPUS & google search engine. The search was done using different key words like Plants, extracts, Alzheimer's disease, Anti-Alzheimer's activity, Anti-Alzheimer's Effect. The published articles were screened for the Anti-Alzheimer's activity & selected articles were included based on the relevance & need of the review. Fig.1 shows graphical presentation of methodology implemented.

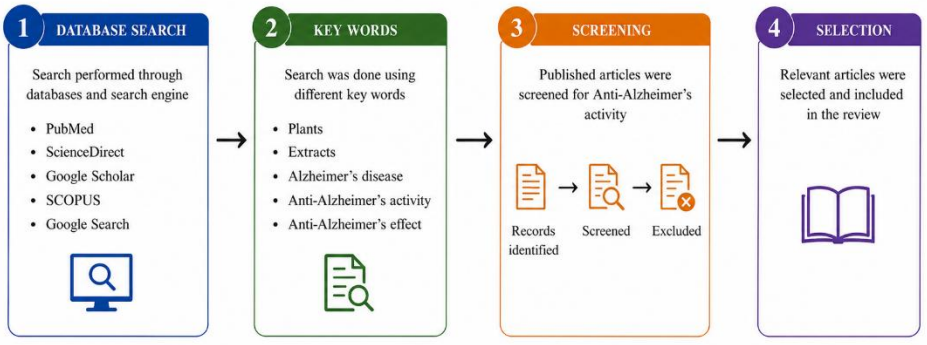

Fig. 1. Methodology for exploring the Anti-Alzheimer's Potential of Medicinal Plants

RESULT & DISCUSSION:

Extraction of Medicinal Plants:

As shown in Fig. 2 anti-Alzheimer's activity of medicinal plants performed using different plant parts, solvents & extraction methods. Different parts of the plants can be used for activity study reveals leaves are most commonly used plant part while other parts like Arial part, flower, whole plant, and fruit are also used. Extraction was performed using solvents like ethanol, methanol, aqueous, chloroform, n-Hexane. Ethanol was found to be preferred solvent in most of the investigations. Maceration method for the extraction was preferred in extraction as it have advantages like suitable for heat sensitive compounds, low cost, energy efficient.

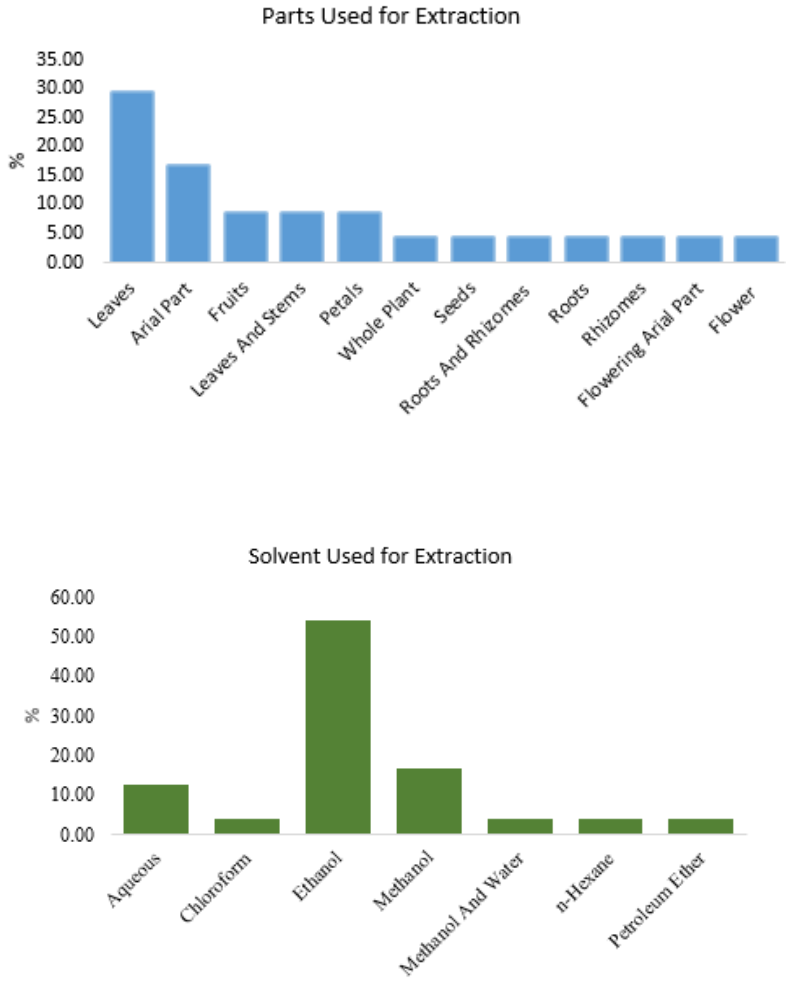

Fig. 2. a) Parts used for extraction b) Solvent used for extraction

Table 1. Plants with Potential Anti Alzheimer's Activity

Plant Name	Family	Part	Extraction	Solvent	Method of Activity	Chemical Constituent	Result	Ref.
Salvia officinalis	Lamiaceae	Aerial parts	Counter-Current Extraction	Ethanol	Conditioned Avoidance Test, Y-maze Spontaneous Alternation Test, Elevated Plus Maze, Morris Water Maze	Rosmarinic acid, Carnosic acid & Carnosol	Extract shown dose dependent effect in all models	32
Piper nigrum	Piperaceae	Fruits	Maceration	Methanol	Y-Maze Task, Radial Arm-maze Task	-	The antioxidant brain status was restored by methanolic extract of P. *nigrum* fruits	33
Echium amoenum	Boraginaceae	Petals	Lyophilized extracts	Aqueous	Morris Water Maze Task	-	Plant extract improved AD biochemical and pathophysiological signs significantly	34
Rosa damascena	Rosaceae	Petals	Maceration	Aqueous	Single-trial Passive Avoidance Test, Morris Water Maze,	Furfural, Quinic Acid, Geraniol, Citronellal	After administration of extract reduction in escape latency was observed. The plant found to useful as antioxidant	35
Streblus asper	Moraceae	Leaves	Maceration	Aqueous	T-maze Test, Inhibitory Avoidance Test	Isoquercetin, Rutin, Catechin, gallic acid, quercetin, rutin, catechin	SA at different doses had significantly increased latency time, SA extract increase memory impairment	36

Aquilaria subintegra	Thymelaeceae	leaves and stem	Hot Solvent Extraction	Chloroform	AChE Inhibitory Activity Assay	Phenols, Flavonoids, Terpenoids, Alkaloids	The extract may be a potent natural AChE inhibitor	37
***Citrus medica* L. cv.**	Rutaceae	Fruits	Maceration	n-hexane	Bioassay for Anticholinesterase Activity	18 Monoterpenes and 8 Sesquiterpenes	Mono terpenes in plant extract have activity against AchE with IC_{50} value of 621 µg/mL	38
***Phagnalon saxatile* (L.) Cass.**	Asteraceae	Flowering aerial parts	Maceration	Petrolium Ether, Chloroform, Methanol	Cholinesterase Inhibition Assay	Terpenoids, Flavonoids, Hydroquinone Glycosides, and Caffeoylquinic Acid derivatives	BChE wa inhibited by methanolic extract with IC50 523.75 µg /mL, while AchE was unaffected	39
***Potentilla fragarioides* var. major**	Rosaceae	Whole plant	Electric Extractor	Ethanol	Passive Avoidance Test (PAT), Y-maze test, Morris Water Maze Test, In vitro Aβ aggregation assay	Neochlorogenic Acid, Chlorogenic Acid, Polydatin, Isochlorogenic acid A, and Buddleoside	Extract significantly inhibited memory impairment in *in vivo* study. EEPF inhibited Aβ aggregation in concentration-dependent manner	40
***Orthosiphon stamineus* Benth.**	Lamiaceae	Leaves	-	Ethanol	Elevated Plus Maze	Phenols, Flavonoids, Coumarins, Sesquiterpenoi, Cinnamic acid	Extract Improved memory retention as evidenced by the improved inflexion ratio & increase in the step-through latency	41
Cyperus rotundus	Cyperaceae	Rhizomes	Percolation	Ethanol	Morris Water Maze Test	-	Morris test confirmed protective effect of *C. rotundus*	42

							on memory impairment	
***Sapindus emarginatus* Vahl**	Sapindaceae	Seed	Maceration	Ethanol	Elevated Plus Maze, Radial Arm Maze, Y-Maze Test	-	Result showed seed extract involved in sustained memory formation in mice with scopolamine treatment	43
***Amaranthus viridis* Linn.**	Amaranthaceae	Leaves	Soxhlet Extraction	Methanol	Elevated Plus Maze Test, Morris Water Maze Test	-	Significant ($p<0.01$) decrease in transfer latency & escape latency at 200mg/kg & 400mg/kg on day 21.	44
Monsonia angustifolia	Geraniaceae	Aerial parts	Agitation	Ethanol	Morris Water Maze Test, Novel Object Recognition Test Cell Viability Measurement, Aβ Peptide Assay	Justicidin A, 5-methoxyjusticidin A, Chinensinaphthol	Justicidin found to reduce Aβ formation, study proved potential of extract in treatment of AD	45
Rheum Ribes	Polygonacea	Roots and Rhizomes	Maceration	Methanol and Water	Passive Avoidance Test, Water Maze Test. Antioxidant Assays	-	Study revealed *Rheum ribes* extract rescue spatial and passive avoidance memory impairments	46
Dracocephalum moldavica	Lamiaceae	Aerial parts	Maceration	Ethanol	Radial Arm Water Maze, Hisptopathology	Rosmarinic Acid and Quercetin	Extract revelled through behavioural & histopathological study to decrease cognitive dysfunction	47
Asparagus racemosus Linn.	Asparagaceae	Roots	Maceration	Ethanol	Elevated Plus Maze, Passive Avoidance, Novel Object	-	Extract significantly ($P<0.05$, $P<0.01$) decreased retention	48

					Recognition Test, Morris Water Maze Test. Acetylcholinesterase (AChE) activity		transfer latency decreased escape latency. significantly (P<0.05, P<0.01) decreases the AChE activity in the brain	
Annona atemoya	annonaceae	Leaves	Electric Extractor	Ethanol	Passive Avoidance Test, Y-Maze Test. Free Radical Scavenging Activity, Aβ Aggregation Assay	Rutin, acetogenins, alkaloids, flavonoids, terpenes	Considering its biological activity and compound profile, Rutin may serve as a promising bioactive agent in AD	49
Orthosiphon stamineus	Lamiaceae	Leaves	Maceration	Ethanol	Elevated Plus Maze, Passive Avoidance	-	study demonstrated that extract effective in AD	50
Enhydra fluctuans	Asteraceae	Stems and Leaves	Cold Extraction	Methanol	Estimation of Anticholinesterase Activity, Antioxidant activity	Tannins, Phenolics, Flavonoids, Phytosterols, Saponins	Greater inhibition of acetylcholinesterase & butyrylcholinesterase enzymes was observed with chloroform extract & also it shown highest antioxidant activity	51
***Bacopa monnieri* (L)**	Scrophulariaceae	Aerial parts	Percolation	Ethanol	Morris Water Maze Test, Choline Acetyltransferase and Immunohistochemistry, Histopathology	-	*Bacopa monnieri* extract could mitigate the memory impairment and the degeneration of neurons, improved the escape latency time in Morris water maze test	52

Euonymus alatus	Celastraceae	Leaves	Maceration	Ethanol	Passive Avoidance Test, Morris Water Maze Task, Y-Maze Task	-	Different behavioural deficit upgraded by extract, reflected in all tests	53
Kigelia africana	Bignoniaceae	leaves	Maceration	Methanol	Rotor-rod Test, T-Maze Test, Wire Hang Test	Gallic acid, Catechin, Chlorogenic Acid, Caffeic Acid, Ellagic Acid, Rosmarinic Acid, Rutin	Extract produced improvement in neurobehavioral abnormalities, cerebral oxidative stress, neurochemical disturbances Induced by $AlCl_3$.	54
Echinacea purpurea	Asteraceae	Flower	Maceration	Ethanol	Y-Maze Test, Forced Swim Test, Novel Object Recognition Test, Anticholinesterase Activity	-	Aqueous & Alcoholic extracts of EP inhibited cholinesterase, restored oxidative balance, also postpone neuronal damage when regularly administered.	55

***In Vivo* Studies:**

Different *in vivo* methods employed to investigate anti-Alzheimer's activity of medicinal plants are highlighted in Table1. *In vivo* models are Conditioned Avoidance Test, Y-maze spontaneous alternation test, elevated plus maze, Morris water maze, T-maze test, passive avoidance test, novel object recognition test, rotor-rod test. Scopolamine[32], aluminium hydroxide[35], streptozotocin[47] used to induce the Alzheimer's disease & activity evaluated using different behavioural tests and found to have significant activity in terms of cognition and memory.

***In Vitro* Studies:**

Anti-Alzheimer's activity of medicinal plants emphasised in table 1 revels the use of *in vitro* methods & its effectiveness. Medicinal plant *Aquilaria subintegra*[37], *Citrus medica* L. cv.[38], *Phagnalon saxatile* (L.) Cass.[39], *Asparagus racemosus* Linn.[48], *Enhydra fluctuans*[51], *Echinacea purpurea*[55] revealed the acetyl cholinesterase inhibitory activity. *Potentilla fragarioides* var. major[40], *Monsonia angustifolia*[45] and *Annona atemoya*[49] revelled the effect on Aβ aggregation by in vitro method. Many of the plants in table 1 found to have the potential antioxidant activity evaluated by different in vitro methods which support the protective antioxidant effect of the plant on neurons.

Possible Mechanism of Actions:

Medicinal plants evaluated for the Anti-Alzheimer's activity shown significant effect on the cognition and memory evaluated by different behavioural tests[42-47].

Possible mechanism of action for the plant is found to inhibit the enzyme cholinesterase which play key role in breaking down of acetylcholine required for learning and memory. Level of acetylcholine in Alzheimer's disease is increased leading to improvement in learning & memory. *Bahrani et al*.[37] investigated the effectiveness of the plant Aquilaria *subintegra* in inhibition of acetyl cholinesterase containing kaempferol with ability to inhibit enzyme through probable binding with anionic or esteratic site on enzyme. Another reason for neuronal degeneration in AD is inflammation of the neurons, many plants found to exhibit anti-inflammatory activity resulting in to neuronal protection & improvement of AD condition. *F. Conforti et al.*[39] demonstrated anti-inflammatory effect & ability of the plant *Phagnalon saxatile* (L.) Cass. to inhibit the NO as mediator of inflammation in macrophages.

Pathogenesis of AD revels involvement of Amyloid-beta (Aβ) plaques and neurofibrillary tangles, medicinal plants study reveals the ability of the plants to prevent the formation of these contributors. *E. Sohn et al.*[40] observed dose dependent effectiveness of *Potentilla fragarioides* var. major to prevent aggregation of Aβ plaques. Antioxidant activity also supports the ability of plant to prevent oxidative stress due to aggregation of Aβ. Presence of antioxidant components in medicinal plants plays significant role as protective role. Plants with additional antioxidant activity are found to have protective effects on the neuronal degeneration in AD. Reactive oxygen species plays important role in pathogenesis of AD and its related complications affecting memory & learning. Plant with antioxidant activity are proved to effective in improvement of AD. *Lalitha Vivekanandan et. al.*[43] demonstrated antioxidant potential of *Sapindus emarginatus* Vahl in dose dependent manner affecting enzymatic and non-enzymatic antioxidant.

Toxicity Study of Medicinal Plant:

Toxicity study of the plants having Anti-Alzheimer's activity are summarized in table 2 with its LD_{50}. The plants *Vigna radiate*, *Vigna pilosa, Salvia officinalis, Salvia officinalis, Asparagus racemosus Linn.* Found to have the LD_{50} value greater than 2000 mg/kg[27,28,32,48] while *Solanum lycopersicum* shown LD_{50} value greater than 2000 mg/kg[24]. Two plants *Cyperus rotundus and Dracocephalum moldavica* shown LD_{50} value greater than 5000 mg/kg while *Cucurbita pepo* shown LD_{50} value greater than 2 g/kg.

Table 2. Toxicity study of plants having Anti-Alzheimer's activity

Name of Plant	LD_{50} (mg/kg)	Reference
Cucurbita pepo	> 2 g/kg	22
Solanum lycopersicum	>3000	24
Vigna radiate and *Vigna pilosa*	>2000	27
Salvia officinalis	>2000	28
Salvia officinalis	>2000	32
Cyperus rotundus	>5000	42
Dracocephalum moldavica	>5000	47
Asparagus racemosus Linn.	>2000	48

Photochemistry of Medicinal Plants:

Phytochemical study reveals the presence of polyphenol, flavonoids, monoterpenes, sesquiterpenes are most prominently accountable for the Anti-Alzheimer's activity in different plant extracts. Polyphenols and flavonoids are considered to be prominent phytoconstituents responsible for neuroprotective action in AD. Tannins, phenolic, flavonoids, phytosterols, saponins may responsible for its effectiveness in AD[35-41]. The polyphenol quinic acid might be responsible for the antioxidant & acetyl choline esterase inhibitory property protecting neurons, also geraniol is one of the approved Antioxidant[35]. The oxidative stress in AD may be reduced by some favonoids quercetin, isoquercetin, and rutin as these are antioxidant[36]. Some flavonoids like luteolin found to have inhibitory activity on the enzyme acetyl choline esterase[39]. The other flavonoid like kaempferol may acts by the inhibitory effect on the acetyl choline esterase enzyme[37]. Monoterpenes also seems to play crucial role as antioxidant which prevent oxidative damage to the neurons in AD, monoterpenes, particularly to limonene, γ-terpinene, geraniol, nerol may be responsible for its effectiveness as antioxidants in AD [38]. Chlorogenic acid may be responsible for its ability to inhibit Aβ aggregation protecting the neuronal damage & progression of AD[40].

CONCLUSION:

The medicinal plant due to its relative safety, affordability and broad action attracts researchers to explore its therapeutic benefits. Many medicinal plants demonstrated the cognitive enhancement and neuroprotective effect in animal models including scopolamine-induced amnesia, aluminum chloride-induced neurotoxicity. Limitations for *in vitro* study highlights a critical gap in mechanistic understanding. Potential of medicinal plants as treasured reservoir highlighted from its important phytoconstituents such as polyphenol, flavonoids, monoterpenes, sesquiterpenes. Phytoconstituents were found to exhibit activity thorugh attenuation of oxidative

stress, acetylcholinesterase inhibition, and interference with amyloid-beta aggregation pathways.

To advance their clinical relevance, future research must emphasize isolation and structural characterization of active compounds, supported by robust *in vitro* and *in vivo* evaluations. Additionally, comprehensive toxicological and pharmacokinetic assessments are essential to ensure safety and therapeutic viability. Ultimately, well-structured clinical trials will be pivotal in translating these phytotherapeutic candidates into effective, evidence-based interventions for Alzheimer's disease.

CONFLICT OF INTEREST:

The authors have no conflicts of interest regarding this investigation**.**

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