Review Article

Taxonomic Distribution of Medicinal Plants for Alzheimer’s Disease: A Cue to Novel Drugs

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Received 27 December 2019; Accepted 14 May 2020; Published 19 June 2020

Academic Editor: Francesco Panza

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Alzheimer’s disease (AD) is a neurodegenerative disorder manifested by decline in memory and mild cognitive impairment leading to dementia. Despite global occurrence of AD, the severity and hence onset of dementia vary among different regions, which was correlated with the customary use of medicinal herbs and exposure level to the causatives. In spite of execution of versatile therapeutic strategies to combat AD and other neurodegenerative diseases, success is only limited to symptomatic treatment. The role of natural remedies remained primitive and irreplaceable in all ages. In some examples, the extracted drugs failed to show comparable results due to lack of micro ingredients. Micro ingredients impart a peerless value to natural remedies which are difficult to isolate and/or determine their precise role during treatment. A variety of plants have been used for memory enhancement and other dementia-related complications since ages. Acetyl choline esterase inhibition, antioxidant potential, neuroprotection, mitochondrial energy restoration, and/or precipitated protein clearance put a vast taxonomic variety into a single group of anti-AD plants. Secondary metabolites derived from these medicinal plants have the potential to treat AD and other brain diseases of common pathology. This review summarizes the potential of taxonomically diverse medicinal plants in the treatment of AD serving as a guide to further exploration.

1. Introduction

Alzheimer’s disease (AD) is a progressive neurodegenerative disorder characterized by personality and behavioral impairments along with dementia [1]. AD is a condition of high neurofibrillary tangles and β-amyloid level due to duplication or mutation of β-amyloid precursor proteins (APP) and a presenilin-encoding gene for proteolytic enzymes [2]. Brain neurodegeneration and β-amyloid (Aβ) deposition are used as biomarkers for the identification of individuals at risk of AD [3]. Neurodegenerative disorders occur due to combined effects of environmental and genetic factors accompanied by aging [4]. AD takes years to progress without apparent clinical symptoms which ultimately lead to declined cognition [5, 6]. AD starts with changes in normal functions of the brain, initially by failure to generate new memories as it is difficult to consolidate new information and leads to rapid forgetting [7]. It is characterized by the formation of plaques followed by inflammation, lack of cholinergic activity, and stress [8]. Risk of cognitive aging and Alzheimer’s disease increases due to inflammation in the central nervous system (CNS) caused by any alterations in the microglia [9].

In a normal physiological state, the oxidative stress is overcome by antioxidant enzymes, but in AD, these enzymes
fail to perform their normal function in the brain [10]. Progression of pathology in AD starts from the perirhinal region to the hippocampus complex and ultimately to temporal lobes with the basal forebrain [11]. AD is mostly linked with emotions, and it affects the quality of life of patients and the caregivers. Changes in behaviors either positive or negative are an important parameter to assess the quality of life of patients suffering from AD [12]. Aging, education, gender, genetics, and apolipoprotein E ε4 allele are significant risk factors for AD [13]. Cardiovascular disease, diabetes, and smoking increases the risk of AD and dementia [14, 15].

Screening and management of cardiovascular diseases like stroke, blood pressure, and other problems significantly lowered the risk of AD [14] contrary to the earlier concept that cardiovascular risks, trauma, smoking, family history, alcohol, and use of nonsteroidal anti-inflammatory drugs (NSAIDs) have no significant impact on AD [12]. Occupational environment, physical exposure, or chemicals also have no relation to progression of AD [16]. Common cognitive activities such as reading books, watching television, and playing games reduce the risk of AD and dementia [17]. Cardiac medications, for instance, digoxin, antihistamines, and other nonpsychotropic agents, may induce cognitive impairment by interfering with neurotransmitter function [18].

The number of people suffering from AD and dementia is increasing globally due to many factors including growing population, aging, and growth. It has been estimated that this number doubled from 1990 to 2016 [19], and currently, an estimated 40–50 million people are affected by dementia [19]. Alzheimer’s disease and dementia share approximately 2.5% of the total mortality toll among the 12% of global deaths caused by neurological disorders [20], and the rate of deaths due to dementia elevated by 148% between 1990 and 2016 making it the fifth largest cause of death [19]. With 7.7 million new cases each year [21], it is predicted that by the year 2050, one out of 85 people will be suffering from Alzheimer’s disease or other forms of dementia. AD is widespread in older people with a 25-50% higher prevalence rate than the young people [22]. Early detection and appropriate treatment are suggested to lower the increasing incidence of AD as well as other metabolic disorders [23]. Age is considered one of the most important factors as dementia is more prevalent in the geriatric population and more than three-quarters of dementia occur as a result of AD [24]. The early onset before age 65 years is very scarce, and its prevalence before age 50 years is even less than 1 per 4000, with roughly 30% of cases being attributed to Alzheimer’s disease [25]. The increasing prevalence of AD has raised concerns to understand its pathophysiology and the risk factors associated with AD to format an affordable preventive or curative strategy. Aging, sex, and genetics are the prime risk factors, but modifiable factors like lifestyle and certain treatable medical conditions play an important role in AD development [26].

An AD brain shows agglomeration of hyperphosphorylated tau protein (neurofibrillary tangle formation), a primary marker of AD, along with deposits of β-amyloid in the gray matter of the brain which ultimately leads to loss of neurons in the brain which causes cognitive impairment leading to Alzheimer’s disease as shown in Figure 1 [3]. β-Amyloid accumulation activates immune cell infiltration resulting in inflammation. This not only hinders cell communication but also leads to cognitive impairment and neuronal cell death. The proteases butyrylcholinesterase (BChE), acetylcholinesterase (AChE), and β-amyloid secretase-1 (BACE-1) correlate with the aggregation and accumulation of β-amyloid plaques in the AD patients’ brains [27]. The genetic component (60–80%) and the apolipoprotein E (APOE) gene are among the leading genetic risk factors [28]. Mutations in genes like presenilins (PSEN I, PSEN II) and APP are involved in the early onset of AD while the APOE gene is considered one of the most important causative genes. Overexpression of the APOE gene causes accumulation of high amount of β-amyloid, and this observation leads to the formation of β-amyloid hypothesis of AD [29]. In mitochondria, redox-active metals interact with oxidative response elements, which generates high levels of hydrogen peroxide that cause oxidative damage. In the early stage of the disease, β-amyloid and tau protein deposition compenstates and downregulates this damage. But when the disease progresses, antioxidant activity becomes decreased which leads to the generation of reactive species that cause high oxidative stress in AD [30]. Decrease in acetylcholinesterase activity occurs when there is excessive deposition of tau protein and β-amyloid adding the complications in AD [31]. Leukotriene signaling inhibition in the brain cells is associated with neuroinflammation and neurodegeneration inhibition, and targeting the leukotriene signaling system will mediate several aspects of AD pathology [32]. Proper and effective diagnosis for AD is done through a postmortem brain study. Currently, new ways are developed to check levels of β-amyloid and tau proteins in blood and cerebrospinal fluid (CSF), but these ways are not reliable so better options need to be developed [33].

Appropriate therapeutic and preventive strategies may delay the progression of AD [34]. Lifestyle modifications and appropriate physical activity can reduce the overall prevalence of AD [35]. Interventions for the management of dementia are not signed up to the mark, and cost-effective programs should be started for better treatment and prevention of dementia [1]. β-Amyloid levels, tau proteins, and genetic susceptibility, along with vascular changes and hearing loss, are used for the early diagnosis of AD. Magnetic resonance imaging (MRI) and positron emission tomography (PET) scanning improved the diagnosis of AD [36]. Due to the complex nature of AD, no reliable treatment is currently available to cure this disorder. The available drugs are used to slow down the progression of the disease and have many side effects [37]. Traditionally, memory and cognitive abilities are enhanced by various plants and their preparations. Plants contain secondary metabolites which possess therapeutic potential in Alzheimer’s disease. This review article will provide us the basis for the development of drugs derived from natural sources both in terms of activity and in terms of cost-effectiveness in the treatment of AD. Secondary metabolites derived from medicinal plants showed potential against dementia and AD [8]. Moreover, natural products have diversity in terms of their structure and functions, so it is easy to develop anti-AD medicines from natural sources. Herbs have therapeutic potency, AChE
inhibitory activity, antioxidant and anti-inflammatory capacity, and redox metal-chelating activities, inhibit $\alpha$-amyloid aggregation, and hyperphosphorylate tau proteins [38].

However, only a few medications have been developed yet that are approved by the FDA for treatment against AD [39]. We focused on the recent studies regarding the potential of various plants and their phytochemicals in treating Alzheimer’s disease. Therapeutic potential of different plant families according to their antioxidant, anti-inflammatory, neuroprotective, and anti-AChE properties is discussed and shown in Table 1 [40, 41] and Figure 1.

2. Material and Methods

2.1. Search Strategy and Selection. The current review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [42]. The published studies were searched by using the MeSH terms “medicinal plants for Alzheimer’s disease”, “Alzheimer’s disease”, “Plants and medicinal used in Alzheimer’s disease”, “role of medicinal plant in Alzheimer’s disease”, “Alzheimer’s disease and treatment approaches”, “new molecules in Alzheimer’s disease”, “medicinal plants and Alzheimer’s disease”, “exploration of Alzheimer’s disease”, “plants family and its use in Alzheimer’s disease”, and “taxonomic distribution of plants in Alzheimer’s disease”, in Google Scholar, PubMed, Ovid, Alzheimer’s disease journals, MEDLINE, Embase, and the Cochrane Database of Systematic Reviews without language limitation, with the last search being updated in 2018. The reference lists were hand searched for other relevant publications.

2.2. Data Extraction/Inclusion and Exclusion Criteria. The first author name, year of publication, source of plants, and plants used in Alzheimer’s disease were selected from each publication according to the following inclusion criteria: (1) plants studied in Alzheimer’s disease; (2) the molecular mechanisms explored in Alzheimer’s disease; and (3) the studies evaluated by limitations, consistency, directness, precision, and publication bias and having control or placebo groups. The quality of the included studies was determined according to the GRADE process, and those articles were included which were published in indexed journals.

3. Results and Discussion

Over the years, the management of AD has remained a big challenge for medical science due to the unavailability of a large number of therapeutic choices; as of today, only a few medications have been developed and approved from the US FDA. Keeping in view the diversity in structures and
Table 1: Medicinal plant species used for the treatment of Alzheimer’s disease.

| Serial no. | Family       | Plants name                        | Part used         | Properties                                      | Chemical constituents                              | References |
|------------|--------------|-----------------------------------|-------------------|-------------------------------------------------|---------------------------------------------------|------------|
| 01         | Acanthaceae  | Thunbergia grandiflora Roxb       | Leaf extract      | Antioxidant, antioxidant, antilipoxygenase, AChE inhibitor | Iridoids, glycosides                               | [44]       |
| 02         | Acoraceae    | Acorus calamus L.                 | Plant extract     | Antioxidant, AChE inhibitor                      | Phenolics, flavonoids                              | [46]       |
| 03         | Anacardiaceae| Mangifera indica Wall             | Leaf extract      | Antipyretic, AChE inhibitor                      | Flavonoids, phenols                               | [48]       |
| 04         | Apiceae      | Semecarpus anacardium Buch.-Hamis.| Leaf extract      | Antioxidant, anti-AChE                         | Flavonoids, phenols                               | [49]       |
| 05         | Apocynaceae  | Hancornia speciosa Gomes          | Fruit extracts    | Antioxidant, AChE inhibitor                      | Flavonoids, phenols, tannins                      | [55]       |
| 06         | Araliaceae   | Eleutherococcus leucorrhizus var. | Leaf extracts     | Antioxidant, adaptogen, anti-inflammatory        | Eleutherosides                                     | [58, 59]  |
|            |              | setchuensis (Harms) C. B. Shang & J. Y. Huang and Eleutherococcus sessiliflorus (Rupr. & Maxim.) S. Y. Hu |              |                                                 |                                                   |           |
|            |              | Acanthopanax trifoliatus (L.)     | Whole plant extract | Leukotriene signaling pathway inhibitor         | Polyphenols, flavonoids                           | [59]       |
|            |              | Voss and Eleutherococcus senticosus Maxim | Root extract | Neuroprotective                                  | Ginsenosides, gintonin                           | [61–63]   |
| 07         | Areceae      | Syagrus romanzoffiana (Cham.)     | Leaf and fruit extract | AChE inhibitor                                  | Stilbenoids, flavonoids, lignans, phenols, and fatty acids | [64]       |
| 08         | Boraginaceae | Nonea micrantha Boiss. & Reut.    | Whole plant extract | Antioxidant, AChE inhibitor                      | Saponins                                          | [66]       |
| 09         | Buxaceae     | Sarcococca saligna Müll.Arg       | Whole plant extracts | AChE inhibitor                                  | Steroidal alkaloids                               | [67]       |
|            |              | Sarcococca hookeriana Baill       | Whole plant extracts | Butylestrase inhibitor                          | Steroidal alkaloids, saligenamide                | [69]       |
|            |              | Buxus papillosa C.K. Schneid      | Leaf extract      | Skin protectant                                  | Vegainine, hookrianaamide, buxakarachiamine      | [70]       |
| 10         | Convolvulaceae| Convolulus pluricaulis Choisy     | Leaf extracts     | Antioxidant, muscarinic receptor stabilizer     | Ascorbic acid, flavonoids, rivastigmine, terpenoids, steroids | [72]       |
| 11         | Crassulaceae | Rhodiola rosea L.                 | Root and rhizome extract | Anti-inflammatory and adaptogenic, antioxidant | Glycoside salidroside                            | [58, 76]  |
| 12         | Cucurbitaceae| Caryocar coriaceum Wittm.         |                  |                                                 | Flavonoids                                         | [77]       |
| Serial no. | Family               | Plants name                     | Part used        | Properties                                      | Chemical constituents | References |
|-----------|----------------------|---------------------------------|------------------|-------------------------------------------------|-----------------------|------------|
| 13        | Fabaceae             | Bauhinia forficata Link and Copaifera langsdorffii Desf | Fruit extract    | Antioxidant, antifungal and antileishmaniasis  | Polyphenols           | [79–82]    |
| 13        | Fabaceae             | Clitoria ternatea L.            | Leaf and root extracts | Antioxidant, hypoglycemic, Brain tonic antioxidant, muscarinic receptor stabilizer | Quercetin and myricetin glycosides | [72]       |
| 14        | Ginkgoaceae          | Ginkgo biloba L.                | Leaf extracts    | Antioxidant, AChE inhibitor                     | Terpenes, bilobalide, ginkgolide | [84]       |
| 15        | Iridaceae            | Crocus sativus Ten              | Dry stigma powder | Antioxidant, neuroprotective                    | Crocin, crocetin, picrocrocin, and safranin | [84]       |
| 16        | Lamiaceae            | Mentha piperita L., Salvia longifolia Nutt., Betonica officinalis L., Satureja montana L., Teucrium L., Chamaedrys Moench, Clerodendrum cephalanthum subsp. montanum (Thomas) Verdc., Teucrium polium L., and Thymus vulgaris L. | Arial part and leaf extracts | Antioxidant, AChE inhibitor, anticholinesterase activity | Carotenoids, phenolic acids, rosmarinic acid, chlorogenic acid, caffeic acid, ferulic acid, Trolox | [92]       |
| 16        | Lamiaceae            | Lavandula angustifolia Mill     | Arial part extract | Antioxidant, neurotransmitter, antianxiety, hypnotic, anticonvulsant | Linalool, tannins, linalyl acetate, camphor, coumarins, triterpenes, flavonoids | [94, 95, 130] |
| 17        | Lessoniaceae         | Ecklonia cava                   | Seaweed extract  | AChE inhibitor, antioxidant, anti-inflammatory, and anticancer | Dieckol, phlorofurofukoecokol-A | [97]       |
| 18        | Lythraceae           | Lawsonia inermis L.             | Leaf extract     | Antioxidant, nootropic potential                | Phytol, pseudoephedrine, aspidofractinine-3-methanol, phenol, 2,6-bis(1,1-dimethyllethyl)-4-methyl, methylcarbamate | [98]       |
| 19        | Lycopodiaceae        | Lycopodiella cernua (L.) Pic.Serm, Lycopodiella riosioid (Sodiro) B.Öllg, Lycopodium clavatum f. brevipedunculatum Louis-Marie, and Huperzia selago var. serrata (Thunb.) A. Löve & D. Löve | Whole plant extract | AChE inhibitor, antioxidant, AChE inhibitor | Huperzine A | [99, 100] |
| 20        | Moraceae             | Ficus carica L.                 | Mesocarp extract | Antioxidant                                     | C-Sitosterol          | [21]       |
| 21        | Myrtaceae            | Psidium guajava L.              | Leaf and fruit extract | Antioxidant, antidiabetic                       | Linoleic acid         | [103]      |
| 22        | Oleaceae             | Olea europaea L.                | Fruit oil        | Autophagous, antioxidant, anti-inflammatory, neuroprotective | Polyphenols, oleuropein aglycone | [105–107] |
| 23        | Pedaliaceae          | Sesamum indicum L.              | Seed extract     | Antioxidant, AChE inhibitor, neuroprotective    | Sesamin, sesaminol, terpenes, flavonoids | [109]      |
functions, natural products could be the best possible source for developing an anti-AD medication. Research has shown that secondary metabolites obtained from medicinal plants have the potential to be converted into a lead molecule effective against AD. In this review, we have enlisted different plant families based on their therapeutic potential (Figure 1) to treat AD as shown in Table 1 and discussed below.

3.1. Family: Acanthaceae. Dicotyledonous plants with 2500 plant species are included in the Acanthaceae family [43]. *Thunbergia grandiflora* Roxb. commonly found in Bangladesh is an important plant of the Acanthaceae family which contains iridoids, glycosides, isounedoside, and *grandifloric* acid. These compounds possess anti-AChE, antioxidant, and antiarthritic properties. The methanolic extract was analyzed for anti-AChE activities and lipid peroxidation inhibition for antioxidant activities. Results revealed the effectiveness of the *T. grandiflora* leaf extract in the treatment of AD [44].

3.2. Family: Acoraceae. The family Acoraceae contains two species around the globe. *Acorus calamus* L. is a plant of the Acoraceae family which is used in Ayurveda and herbal treatment for centuries. It contains flavonoids, triterpenes, alkaloids, phenols, and saponins [45]. Total phenolic contents from the methanolic extract of *Acorus calamus* L. were determined through the Folin-Ciocalteu micromethod at 760 nm. A 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging assay was also performed at 517 nm, and anti-AChE activity was examined in male rats of the Wistar strain. Positive results were obtained, and it was suggested that total phenolics and antioxidant potential of *A. calamus* make it a probable candidate in the treatment of AD [46].

3.3. Family: Anacardiaceae. Cashew or Anacardiaceae is a family of flowering plants comprising 860 plant species [47]. *Mangifera indica* L. Wall is a noteworthy member of the Anacardiaceae family that possesses antipyretic and antiulcer activities. It has recently been proposed that being a rich

| Serial no. | Family       | Plants name          | Part used       | Properties                                      | Chemical constituents                   | References |
|-----------|--------------|----------------------|-----------------|-------------------------------------------------|-----------------------------------------|------------|
| 24        | Plantaginaceae | *Rehmannia glutinosa* f. lutea | Root extract    | Antioxidant, neuroprotective, anti-inflammatory | Catapols, 5-hydroxymethylfurural, bacapasaponin | [110]      |
|           |              | *Bacopa monnieri* or thyme-leaved gratiola | Leaf extracts  | Antioxidant, antilipoxigenase                  | Brahmine, herpestine                   | [111]      |
| 25        | Polygalaceae  | *Polygala alba* var. tenuifolia S.F.Blake | Root extract    | Antioxidant                                    | Lipopolysaccharides                    | [112]      |
| 26        | Ranunculaceae | *Nigella sativa* L.  | Seed extract    | Anti-inflammatory and antioxidant, AChE inhibitor, neuroprotective | Thymoquinone, phenols                  | [113–115]  |
| 27        | Rhamnaceae    | *Ziziphus jujuba* Lam | Whole plant extract | Antioxidant, immunostimulant, and anti-inflammatory | Flavonoids, polysaccharides, phenolics, terpenes | [117]      |
| 28        | Sargassaceae  | *Sargassum sagamianum* | Seaweed extracts | AChE inhibitor                                  | Plastoquinones, sargachromenol, sargaquinoic acid | [119]      |
| 29        | Saururaceae   | *Saururus chinensis* hort. ex Loudon | Whole plant extract | Antioxidant, anti-inflammatory                  | Flavonoids, alkaloids, α-pinene, cinnamic acid, camphene, safrole, β-caryophyllene, linalool, and humulene | [121, 122] |
| 30        | Solanaceae    | *Withania somnifera* (L.) Dunal | Root extracts   | Antioxidant, adaptogenic, leukotriene signaling inhibitor | Sitoindosides, withaferin               | [125]      |
| 31        | Zingiberaceae | *Curcuma longa* L.   | Rhizome extracts | Neuroprotective, anti-inflammatory, protein hyperphosphorylation inhibitor | Curcumin, flavonoids, phenols           | [127]      |
source of flavonoids, *M. indica* Wall have potential against oxidative stress and can be a suitable candidate for the treatment of AD. *Myracrodruon urundeuva* M. Allemão possess anti-inflammatory and acetylcholinesterase inhibitory activity. The presence of high phenolic contents makes it a good principal component for AD management [48]. *Semecarpus anacardium* Buch.-Hamis. is another member of the Anacardiaceae family that contains flavonoids and phenolics. Extracts of plant leaves were analyzed for antioxidant activity, revealing that the extract possesses antioxidant and anti-AChE activities [49].

3.4. Family: Apiaceae. Apiaceae or Umbelliferae is the 16th largest family of flowering plants. It consists of more than 3700 aromatic plant species in 434 genera [50]. Several plants from this family are reported to possess activity against neurogenerative diseases. The *Ferula asafoetida* H. Karst. aqueous extract showed acetylcholinesterase (AChE) activity-inhibiting property in an in vitro as well as in vivo assay in the nervous system of snail and in the brain of a rat. The resins of *F. asafoetida* possess the potential to inhibit monoamine oxidase B (MAO-B) [51]. The acetylcholinesterase-inhibiting and antioxidant properties of *F. asafoetida* lead to memory enhancement and thus can be employed in the treatment of Alzheimer’s disease and dementia [52].

Neuroprotective effects of the *Coriandrum sativum* L. leaf ethanolic extract (volatile oil) were assessed in the β-amyloid rat model of Alzheimer’s disease. The anxiolytic and antidepressant effects were evaluated in vivo, and the antioxidant property was estimated by the total content of the reduced glutathione in the hippocampus. The experiment revealed that the anxiolytic and antidepressant-like effects decreased catalase activity and increased glutathione levels in the hippocampus of the rat brain. Improvement in these parameters suggests the probable advantage of *C. sativum* in Alzheimer’s disease [53].

3.5. Family: Apocynaceae. The Apocynaceae or dogbane family is a diverse family containing 348 genera of plants [54]. *Hancornia speciosa* Gomes is an important plant of the Apocynaceae family which contains flavonoids, phenols, tannins, and anthocyanidins. Volatile components of the plant exhibit antioxidant properties due to the presence of the phenolic compounds while flavonoids and tannins exhibit cytotoxic activity [55].

3.6. Family: Araliaceae. *Ivy or Aralicaeae* is a family of flowering plants that contains 254 plant species [56]. *Eleutherococcus leucorrhizus* var. setchuenensis (Harms) C. B. Shang & J. Y. Huang and *Eleutherococcus sessiliflorus* (Rupr. & Maxim.) S. Y. Hu are two plants of this family that contain alkaloids and eleutherosides B, B1, E, and E1. Analysis of the plant extracts through spectroscopy and High-Performance Liquid Chromatography (HPLC) revealed that these alkaloids effectively improved cognitive function [57]. The *Eleutherococcus senticosus* Maxim extract was evaluated for its ability to alter gene expression in T98G neuroglia cells to question the relevance of these deregulated genes and the eicosanoid signaling pathway. It was revealed that *E. senticosus* effectively inhibited the leukotriene signaling pathway by downregulating Arachidonate 5-Lipooxygenase-Activating Protein (ALOX5AP), Dipeptidase 2 (DPEP2), and Leukotriene C4 Synthase (LTC4S) gene expression [58]. *Acanthopanax trifoliatus* (L.) Voss is another plant of this family that contains polyphenols and flavonoids as active ingredients. Activity of total flavonoid and phenols was assessed from the decoction of leaves. Significant activity was found against oxidative stress which shows promise in the treatment of AD [59]. *Panax ginseng C.A. Mey* contains various pharmacological activities and has been employed in the treatment of different diseases since ages in China [60]. *P. ginseng* C.A. Mey contains ginsenosides and gintonin that have neuroprotective effects [61]; these properties make *P. ginseng* C.A. Mey an effective candidate in the management of neurodegenerative disorders such as AD and dementia [62].

3.7. Family: Arecaceae. Arecaceae commonly known as the “palm family” consists of 181 genera and 2600 species [63]. Hydroalcoholic extracts of *Symgrus romanziiflora* (Cham.) Glassman leaves and fruits were evaluated for their pharmacological properties and anticholinesterase activity in the rat model of aluminum chloride-induced Alzheimer disease. The plant was found to possess 39 metabolites belonging to different chemical classes, i.e., stilbenoids, flavonoids, lignans, phenols, and fatty acids. Acetylcholinesterase activity was significantly decreased by both extracts, and histopathological changes in the cerebral cortex and cerebellum were improved. These results recommend *S. romanziiflora* Glassman as a promising candidate for AD treatment [64].

3.8. Family: Boraginaceae. The Boraginaceae family is comprised of 2000 flowering plant species [65]. *Nonea micrantha* Boiss. & Reut. is a plant of the Boraginaceae family that is reported to possess important saponins. The methanolic extract of *N. micrantha* was prepared and analyzed by DPPH and ABTS for free radical scavenging properties. The assays expressed significant antioxidant and anti-AChE activities. Thin-Layer Chromatography (TLC) and spectrophotometric analysis further revealed that this plant is rich in many important bioactive compounds that have potential in the treatment of AD [66].

3.9. Family: Buxaceae. The box or Buxaceae family comprises 123 plant species [63]. *Sarcococca saligna* Müll.Arg, an important member of this family, was evaluated for its anti-AChE activity. Five new steroidal alkaloids, namely, salingenamides C, D, E, and F; 2B-hydroxypachysamine-D; axillarines C and F; sarcorine; N-dimethyl Sara codeine; vegainine; 5,6-dehydrosarconidine; 2-hydroxy salignarine; salignenamides C, D, E, and F; 2B-hydroxypachysamine-D; axillarines C and F; sarcorine; N-dimethyl Sara codeine; vegainine; 5,6-dehydrosarconidine; 2-hydroxy salignarine; and 2-hydroxysalignamine, were isolated from the ethanolic extract of the plant. In vitro assessment of these alkaloids exhibited anti-AChE activities. All these results signify the effectiveness of *S. saligna* in the management of AD [67]. *S. hookeriana* Baill commonly known as a hook plant is another species of the Sarcococca genus that contains four new alkaloids hookrikanamides A, (+) hookrikanamide B; and hooksikrikanamides A and B; and hookrikanamides A and is
also reported to possess anti-AChE activities. The ethanolic extract of the plant was purified by column chromatography and TLC. Results showed that the hook plant is effective in the treatment of AD [68]. Buxus papillosa C.K. Schneid contains steroidal alkaloids like buxakarachiamine, buxakashmiramine, and buxahejramine, along with four known bases cycloprotobuxine C, cyclovirbuxine A, cyclomicrophyline A, and semperviraminol which possess acetylcholinesterase as well as butyrase inhibitory activities [69]. The ethanolic leaf extract showed that it is effective in the treatment of various skin ailments as well as neurodegenerative disorders [70].

3.10. Family: Convolvulaceae. The morning glory or Convolvulaceae family comprises 1650 plant species [71]. Convolvulus pluricaulis Choisy, another plant of the Convolvulaceae family, is reported to have ascorbic acid, flavonoids, terpenoids, rivastigmine, and steroids as active compounds. It not only scavenges the free radical but also stabilizes muscarinic receptors. The ethanolic extract of this plant was applied in rats. It was observed that memory and learning ability of the rats were improved; this suggested that this plant can be beneficial in AD therapy [72].

3.11. Family: Crassulaceae. The family Crassulaceae also known as stonecrop or orpine [73] consists of 34-35 genera with approximately 1400 species [74]. Rhodiola rosea L., a member of this family, has shown some promising effects on cognition and physical performance. Transcriptome-wide RNA sequencing was carried out to profile gene expression in T98G neuroglia cells in response to root and rhizome extracts of R. rosea L. It was found that the R. rosea L. extract downregulated the expression of ALOX5AP, DPEP2, and LTC4S genes and thus apprehended leukotriene signaling pathways [58]. R. rosea L. possess high adaptogen properties owing to its bioactive compound glycoside salidroside. It has been reported to produce anxiolytic and antidepressant effects in wild-type adult mice. R. rosea L. effectively reduced oxidative stress and increased antioxidant acetylcholine (ACh) and choline acetyltransferase (ChAT) levels in the cortex of Aβ1-42-injected rats [75]. These results make R. rosea L. a potential pharmacological tool to enhance cognition, balance mood disorders, and treat Alzheimer’s disease [76].

3.12. Family: Cucurbitaceae. The Cucurbitaceae family commonly known as the gourd family comprises 955 plant species [63]. Caryocar coriaceum Wittm., a prominent member of this family, contains phenolics and flavonoids. The most prominent flavonoids were quercetin (QCT), isoquercetin, and rutin. Overall, it was concluded that C. coriaceum has potential antifungal and antileishmaniasis activity and can be a possible addition in AD management [77].

3.13. Family: Fabaceae. The Fabaceae or Leguminosae family is the economically important 3rd largest family of flowering plants with diverse 19000 plant species [50, 63, 78]. Crotalaria ternatea L. is an eminent member of this family that contains quercetin and myricetin glycosides. Leaf and root extracts of C. ternatea behaved as brain tonic owing to their potential in increasing levels of acetylcholine in the brain. Bauhinia forficata Link, a species of the Fabaceae family, is reported to possess hypoglycemic activity and is also involved in the signaling pathway in AD. Changes in insulin metabolism lead to molecular pathogenesis and increase glucose levels in AD patients. Thus, improvement in insulin metabolism enhances cognitive functions in patients with AD. Along with hypoglycemic activity, B. forficata also possess anti-AChE and antioxidant activities [79, 80]. Copaifera langsdorffii Desf, another member of Fabaceae, is known as a protective agent for gastric mucosa, and it also contains polyphenols that possess antioxidant activity. Ethanolic and methanolic extracts of C. langsdorffii have antioxidant activity [81, 82].

3.14. Family: Ginkgoaceae. Ginkgoaceae is a family of the Mesozoic Era. Ginkgo biloba L. is a member of this family which is termed as a living fossil [83]. Chemical constituents of G. biloba include ginkgolides, bilobalide, and ginkgetin and other terpenes. These compounds possess remarkable anti-AChE and antioxidant properties that are useful against AD. Further clinical assessment was suggested for the methanolic extract of G. biloba upon revealing in vitro anti-AChE and antioxidant properties when tested [84].

3.15. Family: Iridaceae. The Iridaceae family belongs to the order Asparagales; this family got its name after iris that means rainbow because of its multiple colors. It includes 66 genera with 2244 species worldwide [63]. Crocus sativus Ten commonly known as saffron was assessed for its efficacy in treating AD. C. sativus contain a diverse set of compounds such as lipids, minerals, polypeptides, vitamins, and carbohydrates. Saffron’s main bioactive ingredients are crocin, crocetin, picrocrocin, and safranal [85]. C. sativus dry powder was administered in AD patients aged 55 years for 3 months, and an improvement in cognitive functions was observed. C. sativus was as effective as donepezil in AD patients [86]. Crocin, the main component of C. sativus, exhibited antioxidant potential by reducing malondialdehyde (MDA) levels [87]. Dry stigma of the C. sativus and the water-soluble corcin have been found effective in neurodegenerative conditions such as dementia and traumatic brain injury. Crocin not only enhances cognition but also protects brain cells. It can be a promising agent for the prevention or treatment of AD [88, 89].

3.16. Family: Lamiaceae. The Lamiaceae or mint family is a large family of flowering plants comprising 236 species which are rich in carotenoids, phenolic acids, and ascorbic acid. Many plants of this family possess antioxidant and anticholinesterase activity that is particularly useful in the treatment of dementia and AD [90, 91]. Antioxidant and anticholinesterase activities of different plants from the family Lamiaceae were assessed. A total of twenty-six plant methanolic extracts were tested, and nine plants, namely, Mentha piperita L., Salvia longifolia Nutt., Betonica officinalis L., Satureja montana L., Chamaedrys Moench, Clerodendrum cephalanthum subsp. montanum (Thomas) Verdc., Teucrium polium L., and Thymus vulgaris L., showed strong (75%) AChE inhibitory activity. These results revealed that plants belonging to
the Lamiaceae family possess strong AChE inhibitory activities as well as antioxidant activities that are useful in the management of AD [92].

The *Lavandula angustifolia* Mill aqueous extract was evaluated for its effect on the spatial performance of AD rats. Promising results were obtained where spatial learning deficits in AD rats were reversed effectively by the lavender extract [93]. Lavender extract treatment reversed levels of 10 metabolite markers nearly to control including carnitine, pantothenate, isobutyrate, glutamine, alanine, isoleucine, serine, valine, glucose, and aspartagine involved in AD pathogenesis. These results established a promising therapeutic potential in *L. angustifolia* in disease improvement and treatment of AD [94]. The aqueous extract of lavender was evaluated for induction of LTP in the CA1 area of the hippocampus in rats. The lavender extract exhibited positive effects on the plasticity of synaptic transmission and thus improved impaired spatial memory in the Alzheimeric animals [95]. These results suggest a potential therapeutic role of lavender in the treatment of AD.

3.17. Family: Lessoniaceae. *Ecklonia cava* Kjellman, an edible brown seaweed, is a member of kelps or the Lessoniaceae family found in oceans of Korea [96]. It contains polyphenols like eckol, dieckol, dieckol, and phlorofurokoeckol-A which possess antioxidant, anti-inflammatory, and anticancer properties. A phenolic extract was made with ethanol at 50°C and then evaporated until a gummy paste is formed and further separated by ethyl acetate and water. Amyloid biosynthesis, anti-AChE, glycogen synthase kinase 3β-amyloid inhibition, and BACE inhibition-1 assays were performed. Results showed that dieckol and phlorofurokoeckol-A were effective against AChE and amyloid precursor protein biosynthesis that could be helpful in the treatment of AD [97].

3.18. Family: Lythraceae. The Lythraceae family includes 32 genera and 620 species of herbs, shrubs, and trees [86]. Phytochemical characterization of *Lawsonia inermis* L., a species that contains twelve various compounds, was performed in the chloroform extract of leaves. Swiss albino mice were tested for memory-enhancing and cognitive function peroral administration of *L. inermis* powder. Memory loss due to oxidative neurodegeneration was effectively reversed by *L. inermis*. The exact mechanism of this reversal is not known; however, the antioxidant potential is accounted for the nontropic potential of the plant [98].

3.19. Family: Lycopodiaceae. The Lycopodiaceae family is an important family of vascular plants which is reported to contain various alkaloids, flavonoids, and phenolic compounds that possess antioxidant and anti-AChE activities. Huperzine A is mainly involved in anti-AChE activities. Extracts of different species from the Lycopodiaceae family like *Huperzia flexibils* (Fée) B.Øllig, *Lycopodiella cernua* (L.) Pic.Serm, *Lycopodium clavatum* f. brevipedunculatum Louis-Marie, and *Lycopodiella riofrioi* (Sodiro) B.Øllig were analyzed by liquid Chromatography-Mass Spectroscopy (LC-MS) and TLC. *L. clavatum* showed strong anti-AChE activity [99]. *Huperzia selago* var. serrata (Thunb.) A. Löve & D. Löve contains huperzine A as an active constituent which has potent anti-AChE activity. Safety, tolerability, and efficacy of *H. selago* var. serrata were tested on 210 AD patients, and no significant side effects were obtained [100].

3.20. Family: Moraceae. The Moraceae family, commonly known as the fig or mulberry family, is cosmopolitan in nature and is comprised of 38 genera and over 1100 species [63]. *Ficus carica* L. generally called fig possesses a remarkable antioxidant nutritional value conferring it a great protective mechanism against various ailments and AD. The bioactive metabolites in *F. carica* mesocarp were assessed for their effect on the human neuroblastoma SHSY5Y cell line via a cell viability test. Nuclear magnetic resonance (NMR) spectroscopy profiling active metabolites was carried out, and it was revealed that c-sitosterol, an alphatic compound, is responsible for neuronal bioactivity [21].

3.21. Family: Myrtaceae. It is a dicotyledonous family widely distributed in tropical and warm temperate regions comprising 5950 plant species [63, 101, 102]. *Psidium guajava* L. commonly known as guava is the most prominent member of this family that possesses high antioxidant as well as anti-diarrheal and anti-diabetic potential. The leaf extract of guava was analyzed for antioxidant properties in a linoleic acid system by a thiocyanate method. A radical scavenging assay was performed with 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulphonic acid) (ABTS*) radicals at 414 nm. Results revealed that guava leaves possess significant antioxidant activity that can be effective in the management of AD [103].

3.22. Family: Oleaceae. The family Oleaceae is comprised of 26 genera and 700 plant species. The family consists of shrubs, trees, and woody climbers which are subcosmopolitan in distribution [104]. *Olea europaea* L., an eminent member of this family, possesses certain promising effects on AD. AD progression is attributed to the accumulation of hyperphosphorylated β-amyloid and tau proteins. Elimination of the damaged organelles and aggregated proteins is carried out by autophagy through lysosomal digestion. Autophagy deficiency leads to ineffective elimination and in turn accumulation of damaged and aggregated mitochondria in the cell. This increases cell toxicity and oxidative stress. Extra virgin olive oil possessed several polyphenols, e.g., oleuropein aglycone, that cause autophagy, thus decreasing aggregated proteins and in turn cognitive impairment. Extra virgin olive oil consumption as supplement can benefit Alzheimer’s patients through the induction of autophagy [105]. *O. europaea* is a rich source of natural antioxidant. The fruit ethanolic extract of *O. europaea* was analyzed for its putative neuroprotective effects in alloxan-induced cognitive impairment in mice. A behavioral study was carried out to assess neuroprotective effects. The administration of olive oil not only altered the mice’s behavior but also decreased lipid peroxidation in the cells [106]. The main bioactive compounds are phenolic oleuropein and hydroxytyrosol (HT) found in the leaf extract, which are responsible for antioxidant, anti-inflammatory, and neuroprotective properties [107].
3.23. Family: Pedaliaceae. Pedaliaceae commonly known as the pedaliun or sesame family is a small family of flowering plants comprising about 79 species [108]. *Sesamum indicum* L. is an important plant of the Pedaliaceae family which contains sesamol that possesses antioxidant and neuroprotective activities mainly in dementia and Huntington disease. It also contains flavonoids, terpenes, alkaloids, and chemicals like sesamin and sesamolin. Different extracts were tested, and it was found that *S. indicum* possess anti-AChE as well as antioxidant activities [109].

3.24. Family: Plantaginaceae. Plantaginaceae is a very diverse family of flowering plants with 1900 plant species [63]. *Rehmannia glutinosa* f. lutea from this family contains catechins and 5-hydroxymethylfurfural, which has been reported to possess antioxidant, neuroprotective, and anti-inflammatory activities. The *R. glutinosa* lutea root extract was analyzed for its neuroprotective effects in vitro in hippocampal neurons, and it showed remarkable activity against AD, but its efficacy is still not well established in humans [110]. *Bacopa monnieri* (L.) Wettst. or thyme-leaved gירתolya is another important plant of this family that possesses antioxidant and antilipoxygenase properties. Various alkaloids like brahmine, herpestine, B-sterols, betulic acid, bacopasaponins (bacopasides A, B, C, I, II, X, and N2), and bacopasaponin E (III, IV, V, and N1) were scrutinized from the leaf extract of *B. monnieri*, and promising results were obtained. These alkaloids improved cognitive function and memory capacity in patients of AD [111].

3.25. Family: Polygalaceae. Polygalaceae is commonly known as the milkwort family with 900 known plant species. Use of *Polygalas alba* var. tenuifolia S.F.Blake, an important plant of the Polygalaceae family, in certain disorders like insomnia and cognitive impairment has been reported. The aqueous extract of *P. alba* var. tenuifolia improved memory and other behavioral disorders in rats. These promising results suggest further research on *P. alba* var. tenuifolia for the effective treatment of AD [112].

3.26. Family: Ranunculaceae. Ranunculaceae is a family of over 2000 flowering plant species in 43 genera and is distributed worldwide commonly known as the buttercup family [63]. *Nigella sativa* L. belongs to the family Ranunculaceae and is reported to possess several phenolic compounds such as stearic acid, linoleic acid, palmitic acid, oleic acid, arachidonic acid, and eicosadienoic acid. *N. sativa* has potent antioxidative effects and can effectively improve scopolamine-induced cognitive impairment and reduced the AChE activity and oxidative stress of the rat’s brain [113]. Thymoquinone, a major component of *N. sativa*, exhibited neuroprotective effects on various neuronal disorders such as epilepsy, Alzheimer’s disease, and neurotoxicity [114]. The increased cognitive functions and neuroprotective effects of thymoquinone (TQ) are attributed to its substantial anti-inflammatory and antioxidant potential [115]. *N. sativa* prevented the damage of the spatial memory in scopolamine administration-induced oxidative stress of the brain tissue in rats [113]. Seeds of *N. sativa* are reported to exhibit positive effects on memory impairment and neurotoxicity [114].

3.27. Family: Rhamnaceae. Buckthorn or Rhamnaceae is a family of 950 flowering plant species [43]. *Ziziphus jujuba* Lam is a plant belonging to the Rhamnaceae family that activates choline acetyltransferase which prevents loss of cholinergic neurons [116]. *Z. jujuba* contains flavonoids, polysaccharides, terpenoids, and phenolics that have antioxidant, immunostimulant, and anti-inflammatory properties. The polysaccharide fraction of the hydroalcoholic extract of *Z. jujuba* displays a promising antioxidant profile that is useful in the treatment of AD [117].

3.28. Family: Sargassaceae. Sargassum, a member of Sargassaceae, is a brown seaweed that possesses compounds like proteins, fibers, and carotenoids and particularly phastoquinones, which possess anti-AChE activity [118]. Four compounds that possess anti-AChE activity were isolated, namely: sargauquinic acid, sargachromenol, dihydro-mono-ofoxarnesyl acetone, and mono-ofoxarnesyl acetone. Enzymatic activity of the methanolic extract of *Sargassum sagamianum* (Yamada) Yoshida & T. Konno and its compound sargauquinic acid was found effective in the inhibition of acetylcholinesterase as well as butyl cholinesterase which is remarkable in the treatment of AD [119].

3.29. Family: Saururaceae. Saururaceae is a small family of flowering plants comprising only four genera and seven species mainly herbaceous plants inhabiting eastern and southern Asia and North America [120]. *Saururus chinensis* hort. ex Loudon, a plant of this family, was assessed for neuroinflammatory responses in BV-2 microglial cells and for antioxidant potential was estimated by DPPH and alkyl radical scavenging assays [121]. Chemistry of *S. chinensis* revealed the presence of flavonoid, fatty acid, alkaloid, quinone, amino acid, and essence oils. Hyperin, isooquer cetin, quercetin, and quercitrin were reported from the stem and leaf [122, 123]. *S. chinensis* showed significant antioxidant and anti-inflammatory activity against tumor necrosis factor-alpha. Quercetin (QCT) was revealed as one of the major constituents of *S. chinensis*. QCT inhibited the excessive release of Nitric Oxide (NO) in Lipopolysaccharide- (LPS-) stimulated BV-2 cells [121].

3.30. Family: Solanaceae. Solanaceae or nightshade is an important family of 27000 flowering plants. Plants of the Solanaceae family contain many important alkaloids that have therapeutic importance [124]. *Withania somnifera* (L.) Dunal, a valuable plant of the Solanaceae family, contains sitoindosides VII-X and withaferin A that has mainly antioxidant activities. The root extract of *W. somnifera* was beneficial in reversing the effects of memory impairment in transgenic mice when it was administered to them for 30 days. These results recommend *W. somnifera* as a good candidate target for the treatment of AD [125]. Anti-inflammatory lipoxin signaling pathways were upregulated by *W. somnifera* (L.) extracts, while proinflammatory signaling pathways (ALOX5AP, DPEP2, and LTC4S genes) were downregulated to inhibit the biosynthesis of prostaglandins, leukotrienes, and thromboxanes [58]. This leads to reduced
neuroinflammation and neurodegeneration, declined tau phosphorylation and β-amyloid plaque load, activation of neurogenesis, elevated neuronal survival, and synaptic integrity, all the pathological hallmarks of Alzheimer disease [32].

3.31. Family: Zingiberaceae. The Zingiberaceae or ginger family is an important family of monocotyledonous flowering plants with 1600 species. Plants in the Zingiberaceae family are also known as pseudostems [126]. Turmeric or Curcuma longa L. is an important plant of this family which is commonly used as a spice and traditionally used in the management of cough, hepatic disorders, diabetes, and inflammations. Turmeric rhizome possesses pharmacological activities and contains curcumin (diferuloylmethane), demethoxycurcumin, and bisdemethoxycurcumin as chemical constituents. Various glycosides flavonoids and terpenoids are reported from C. longa [127]. In another study, it was found that oral administration of curcumin inhibits Aβ fibril deposition and hyperphosphorylation of tau proteins that is an important pathway leading to AD [127]. Extracts of C. longa rhizome upregulated the expression of the prostaglandin E receptor 3 gene and downregulated ALOX12 expression, suggesting a positive role of C. longa which inhibit the neurotoxicity [127].

4. Conclusion
AD is the most prevalent neurodegenerative disease over the entire globe with no effective drugs or therapy to treat the conditions. It appeals for the exploration of new chemical entities where medicinal plants can play a pivotal role being the rich source of pharmacological principles and vast diversity. The secondary metabolites of plants including alkaloids, flavonoids, and phenolic acids play a key role in improving regeneration and/or inhibiting neurodegeneration. Various natural remedies and individual plant parts have shown significant potential in the treatment and management of AD. Diversified medicinal plants of the same taxonomic origin share some common pharmacological properties. This review will provide basis for further exploration of anti-AD drugs by screening unexplored species from the already reported effective families.

Conflicts of Interest
The authors declare that they have no conflicts of interest.

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