Medicinal Plants and Biogenic Metal Oxide Nanoparticles: A Paradigm Shift to Treat Alzheimer’s Disease

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Abstract: Alzheimer’s disease (AD) is the most prevalent form of dementia. Improving the amount of acetylcholine in the brain is an efficient way to treat the illness. The global incidence of dementia is estimated to be as high as 50 million, and it is expected to increase every 20 years until 2040, resulting in a costly burden of disease. Early-life risk factors for pathology include genes, chromosomal abnormalities, head injury, insulin resistance, and inflammation. Potentially modifiable risk factors including obesity, diabetes, hypertension, and smoking are associated with Alzheimer’s disease (AD) and represent promising targets for intervention. The drugs currently being used to manage AD have various drawbacks. The chemical inhibition of cholinesterase enzymes is an effective technique for treating signal related neuropathology, and possible sources of compounds with these properties are natural products and biogenic metal oxide nanoparticles. There is a potential source of AChE and BChE inhibitors in the abundance of plants in nature, and natural goods appear to offer useful medications and templates for the development of other compounds. This dissertation represents a review of the literature on species of medicinal plants and nanomaterial related plants tested for their inhibitory action of AChE and BChE. Plant species and the plant-mediated metal oxide nanoparticles referred to are possible cholinesterase inhibitors and can assist researchers in their study of natural products that may be beneficial in the treatment of AD.

Keywords: medicinal plants; metal oxide; nanoparticles; dementia; Alzheimer’s; cholinesterase

1. Introduction
Alzheimer’s disease (AD) is a multifactorial, advanced, and complex degenerative disorder. The key clinical symptoms found in the central nervous system are inflammatory mechanisms, amyloid plaques, and neurotransmitter disruption. In the basal forebrain, there is a progressive reduction of neurons that contributes to cholinergic hippocampal innervations; these changes can disturb a person’s mental ability and result in neurological disorders along with a loss of memory [1]. Alzheimer’s disease (AD) is most prevalent neurological disorder in adults. It was initially reported by Alois Alzheimer, a 50-year-old lady who suffered from a steady deterioration in mental incapacity, which led to neural degeneration [2]. AD patients can generally be identified by their gradual memory loss, behavioral instability, speaking and walking difficulties due to poor body balance, etc. According to a WHO study, AD impacted 36 million people by 2015 and the economic and
social strains due to AD in industrialized and developing countries is rising annually [3]. Due to a lack of therapeutic and diagnostic tools, AD is treated as one of the fundamental priorities for research in G8 nations. AD comprises 60–80% of worldwide dementia events. According to estimates from 2000 to 2013, 71% of fatalities in the US were attributed to AD, while the remaining fatalities were attributed to diseases like heart attacks, cancer, etc., [4].

The physiology of AD is complex and it involves several pathways. Acetylcholine (ACh), the first neurotransmitter identified, and butyrylcholine (BCh) both play a significant role in memory learning. ACh stimulation of nicotinic receptors appearance is linked with learning ability. When the nerve terminals are depolarized, this releases stored ACh in nerve vesicles that bind to the receptor in the synapse [5]. This occurs due to the occurrence of a huge quantity of acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) enzymes in an AD patient’s brain, which often affect the activity of respective neurotransmitters, reduce the short half-life of ACh and BCh, and lead to AD. These enzymes are detected among neuritic plaques and neurofibrillary tangles [6]. These enzymes cause a loss of stimulatory activity by hydrolyzing the esters bond in ACh and BCh molecules [7]. Despite of the huge efforts of researchers in this context, the therapeutic strategy for AD has mainly been focused on cholinesterase inhibition (based on cholinergic hypothesis) that provides a target for severe or mild AD [8]. It has recently been shown that inhibition of AChE plays a significant role in the induction of cholinergic transmission and also decreases the accumulation of β-amyloid and neurotoxic fibrils in AD [9,10]. Hence, AChE and BChE inhibitors have turned into striking substitutes to AD treatment. Existing anticholinesterase drugs like donepezil, galantamine, physostigmine, and tacrine used for treatment of AD are reported to have many harmful effects like low availability, hepatotoxicity, adverse cholinergic effects, and a short duration of biological action [11,12].

Plants with active substances are becoming new possible medicines for Alzheimer’s disease, in line with the traditional origins of pharmaceutical research. Plant active secondary metabolites not only counter the toxic effect of compounds but also act synergistically with other elements from identical plants to counteract the hazardous effects of AChE and BChE [13]. The history of drug discovery has shown that several plants have been used to cure a number of neural illnesses, including neurodegenerative disorders and neuropathological disorders [14]. A Chinese herbal therapy Yokukansan, which has no side effects, has been used effectively to treat several neurological disorders [15]. The Food and Drug Administration in the US identified galanthamine, an alkaloid derived from snowdrops, for the treatment of Alzheimer’s disease [16]. Nanotechnology, a diverse field, is another possible hotspot to identify various therapeutic strategies including drug delivery across the blood brain barrier for AD. Efficient disintegration of mature fibrils and remarkable inhibition of the β-amyloid fibrillation mechanism were suggested for Terminalia arjuna dependent gold nanoparticles. In addition, gold nanoparticles have also been reported to be successful in inhibiting cholinesterase enzymes, suggesting that gold nanoparticles are neuroprotective [17]. In addition, Trehalose functionalized gold nanoparticles disintegrate matured fibrils and inhibit proteins aggregation [18]. Bacopa monnieri based platinum nanoparticles, as a commendably eradicate reactive oxygen species, tend to drops the ROS level in Parkinson’s disorder [19]. Selenium and other metal oxide nanoparticles are also used effectively for AD on an in vivo and in vitro basis [20].

1.1. Worldwide Prevalence of Alzheimer’s Disease in Aging Populations

Population ageing has become one of the world’s most universal trends. According to the US Center for Disease Control and Prevention and the UN Aging Program, the number of older people (65+ years) in the world is expected to grow from 420 million in 2000 to around 1 billion by 2030 [21]. As a result, developed nations will see a worldwide rise in the number of older persons, ranging from 59% to 71%. AD is expected to trigger major obstacles for public health systems worldwide, as the incidence of AD is closely related to rising ages [22]. According to aggregate statistics from population-based surveys in Europe, the normal rate for dementia is 6.4% for people aged 65+ years [23]. In the US, a study of
the national demonstrative model of people >70 years of age showed a widespread trend. Several papers have associated AD with aging, obviously because AD generally (in about 90% of cases) affects individuals from the age of 65 and its prevalence doubles each 5 years, generating a time-dependent exponential increase [24]. Currently there are 5 million new cases of dementia each year, most of which suffer from AD. At age 65, the prevalence of AD almost doubles every five years [25]. Almost 1 in 10 individuals in developing countries are affected by dementia, while 1/3 of 85 year olds may have dementia related signs and symptoms. For low and middle income countries, a report on AD and dementia estimated that the prevalence of these diseases was 3.4%, which has drawn a lot of interest in recent years. In seven developing countries, the pervasiveness of dementia (DSM-1V criteria) in people aged 65+ years ranged widely from 0.5% to 6%, which is lower than in developed countries, according to the 10/66 Dementia Investigation Group. In rural Latin America and India, the rate of AD ubiquity was approximately a quarter of the rate of European nations. The prevalence rate of AD in people (65+ years) was 3.5% in built-up areas of China, 6.4% in Latin American states, and 5.1% in Sao Paulo in Brazil [26].

1.2. Frequency Rate of AD

In Europe, the collective rate of AD was 19.4 in 1000 persons/year among people aged 65+ years [27]. Shared data was taken from two large-scale communities (Baltimore and Seattle in the US) and the elderly community (65+ years); the data indicated a prevalence frequency of 15.0 (male, 13.0; female, 16.9) in 1000 individuals per years for AD [28]. With increasing ages, the rate of AD increased exponentially for patients until they reached 85 years of age [29]. According to the Cache County Study, the AD rate increased and then at old ages started to decline for both males and females [30]. However, some large scale studies and meta-analyses in Europe provided no rationale for the potential decline in the AD rate among the oldest age groups [31]. Geographical differences seem to have been the main factor in the prevalence of dementia, based on a survey of eight European countries that investigated the higher incidence rates being found in north-western countries than in southern countries among people of old ages [27]. This research study confirmed that the prevalence rate of AD in developing countries is typically lower than in North America and Europe. For example, the incidence rate of AD among people aged 65+ years in India was 3.2 per 1000 per year and 7.7 per 1000 per year in Brazil [32,33].

1.3. Defining Risk Factors of Alzheimer’s Disorder

AD is a multifactorial disorder, for which older age is the most significant factor. A strong correlation between AD and older age may moderately mimic the combined influence of numerous risk and defense factors over a lifetime, including biological factors, the impact of complex genetic vulnerability, psychological aspects, and lifetime environmental exposures. Some of the etiological hypotheses for AD with major risk are provided below [34].

1.3.1. Genetic Assumption

Early development of family AD, which accounts for just around 2% to 5% of all AD patients, is often caused by autosomal dominant modifications, e.g., mutations in amyloid precursor proteins or preseniline 1 and 2 genes. In terms of risk factor profiles and neuropathological characteristics, the majority of cases of AD are periodic and show a large degree of heterogeneity [35]. Lineages of non-demented people have a short lifespan risk of mounting AD compared to the first degree lineages of AD patients. Both environmental and genetic factors contribute towards the phenomenon of AD. However, some studies suggested that knowing hereditary components like apolipoprotein E (APOE) ε4 allele can easily help to describe the familial aggregation of AD and also specified that some other susceptibility genes may be involved [36,37]. For both initial and late onset of AD, APOE ε4 allele is the single most commonly suggested hereditary factor and a susceptibility gene for AD. The risk of AD rises with an increasing number APOE ε4 alleles and the age of AD
commencement decreases in a dose dependent manner. With increasing age, the risk effect of APOE ε4 allele on AD declines, and almost 15% to 20% of AD cases are recognized to be associated with the ε4 allele. A number of additional vascular related applicant genes with varying results, such as cholesterol 24-hydroxylase, Angiotensin-I converting enzymes, and insulin-degrading enzyme genes have been identified [36].

1.3.2. Vascular Pathway Assumption

Evidence from multidisciplinary studies (epidemiologic, neuropathological and neuroimaging studies) supports the assumption that vascular morbidity factors (e.g., diabetes, high blood pressure, white matter lesions) and vascular risk factors (e.g., obesity, smoking, and high cholesterol levels) are linked with a high risk of dementia [38,39].

1.3.3. Alcohol Consumption

Significant alcohol drinkers have shown a three-fold increased threat of dementia and AD in the middle stage of development later in their lives, mostly involving APOE ε4 allele carriers [40]. However, low to modest alcohol intake was associated with a decreased incidence of AD and dementia, which caused the presumption that light to moderate alcohol consumption would protect against AD. However, the role of moderate to light alcohol consumption is highly controversial due to outcome misclassification, high socioeconomic status, and the effects of a healthy lifestyle. Alcohol has numerous valuable impacts on various cardiovascular disorders factors, including inflammatory, lipid and lipoprotein, and hemostatic factors [41]. On the other hand, too much alcohol consumption has a deteriorating effect on the brain and has been related to brain atrophy [42].

1.3.4. High Cholesterol and Usage of Cholesterol-lowering Drugs

High level cholesterol in midlife has a strong association with an increased risk of late life AD and dementia disorders, while at late life there is either no correlation or an opposite association between high cholesterol and a consequent improvement of AD [43]. A bidirectional assembly between the cholesterol level and AD development has indicated that at middle age, high total cholesterol represents a risk factor for AD development while, at late age, decreasing blood cholesterol acts as a marker for AD and dementia [44]. The role of subtype cholesterol (low density lipoprotein, triglycerides, and high density protein) provides little information on AD and dementia disorders. Available clinical and epidemiological records on the use of statins (lipids dropping drugs) and AD risk provides a mixed image. A number of studies have stated that statin consumers have reduced AD prevalence [45]. Meanwhile, others revealed that the use of statins was correlated with a lower threat of AD and dementia independent statins lipophilicity; however, others reported no advantageous influence or a modestly lessened risk of AD with statins use [46]. Statins may also have a variety of valuable tasks in the central nervous system comprising endothelial defense via actions on the nitric oxide synthase system, as well as antioxidant, anti-inflammatory, and antiplatelet effects. Statins also reduced β amyloid secretion in vitro and in vivo [47].

1.3.5. Psychosocial Assumption

An organized study reported that actively integrated lifestyles and psychosocial factors over a life span may reduce AD and dementia risks. These factors comprise primary life educational completion, midlife high workout complication, and participating in mentally and physically motivating activities later in life [48]. Socioeconomic and education status were mostly found to be interrelated when both agencies were studied, so the self-governing connection was identified only with education. Education could improve mental and neural reserves that might provide a compensatory mechanism for deteriorating obsessive changes in the brain and hence interrupts the AD and dementia disorders [49]. After education, physical activity has also been reported to be linked to AD and dementia disorder delays. The chance of developing AD and mental illnesses can also
decrease through low-intensity exercises such as walking [50]. Physical exercise not only encourages brain plasticity, but also promotes general and vascular health, and also affects a variety of neurotrophic factors and gene transcripts that are essential for general and vascular health [51]. In addition, intellectual activities including gardening, knitting, plying board, reading, social, and cultural activities, dancing, and playing musical instruments showed a protective effect and a reduced risk of AD [52]. According to the Canadian Study of Health and Aging, involvement with convoluted work may decrease the risk of vascular dementia and AD.

1.3.6. Lethal Exposure

Consumption of heavy metals like Al from drinking water and heavy metals exposure such as mercury, cadmium, lead, zinc, etc. has been proposed as a high risk factor for AD and dementia, but this has not been confirmed [53]. According to a meta-analysis of epidemiological research, there is a link between Alzheimer’s disease and occupational exposure to extremely low frequency electromagnetic fields (ELF-EMF), which might raise the chance of developing the disease [54].

1.3.7. Inflammation

An increase in the level of serum C-reactive protein (CRP) in midlife was associated with both vascular dementias and Alzheimer’s, signifying that inflammatory markers may imitate both cerebral mechanisms and peripheral diseases which are linked to AD and dementia [55]. Recent research studies reported that long term use of non-steroidal anti-inflammatory drugs (NSAID$_S$) may have a valuable consequence for avoiding dementia and AD [56]. Meanwhile, other research studies found an association between neuritic plaques and inflammatory proteins in the brain. It can be hypothesized that in neurodegeneration processes, the inflammatory mechanism plays an important role. However, no sign was found by neuropathological studies of a correlation between use of NSAID$_S$ and a reduced load of AD pathological variations [57].

1.3.8. Other Factors

First, a meta-analysis of case control studies reported a connection between head injury and the risk of developing AD and dementia [58]. However, other studies suggested that AD was only associated with severe head injury and not with head trauma [59]. Second, an association between a reduced risk of AD and both dementia and hormone replacement therapy had been frequently described until 2004 in several observational studies after a significantly high risk of AD linked with estrogen therapy was found in a women’s health study. Lastly, numerous other studies have stated that a connection exists between AD and dementia with depression, but it is arguable that depression is either a confirmed risk for AD or a preclinical symptom [60].

2. Present Therapeutic Issues and Disadvantages of Alzheimer’s Disease Therapies

Only five drugs for AD have been approved by the Food and Drugs Administration (FDA) for clinical use up to date [61]. In addition, several drugs are in clinical trials such as antiamyloid agents and have not yet been accepted for clinical use. Among the FDA permitted medicines, the only memantine is the GABA receptor modulator, whereas donepezil, tacrine, rivastigmine, and galantimine are cholinesterase inhibitors, as shown in Table 1 [62]. Currently available drugs have inadequate effectiveness, as they cause side effects, only offer limited symptomatic relief, and are expensive [63]. The mentioned shortcomings are due to poor pharmacokinetics, including low bioavailability, oxidation, hydrolysis, volatility, an affinity towards drug-drug communications, and partial transport through the brain blood barrier (BBB) [64].
### Table 1. List of Drugs for Treatment of Alzheimer’s disease in Numerous Stages of Trials.

| S. No | Name and Code of Drug | Manufacturers                  | Stage of Trials | Clinical Identifier Code |
|-------|-----------------------|--------------------------------|----------------|--------------------------|
| 1     | CT1812                | Cognition Therapeutics (Pittsburgh, PA, USA) | Completed       | NCT03522129             |
| 2     | AZD 3293              | AstraZeneca/Lilly (Cambridge, UK) | Phase-2/3       | NCT02040987             |
| 3     | MK-1942               | Woodland Research (Rogers, AR, USA) | Phase-1         | NCT04308304             |
| 4     | PF-04360365           | Pfizer (New York, NY, USA)    | Phase-2         | NCT00945672             |
| 5     | Bexarotene            | Cleveland Clinic Lou (Los Vegas, NV, USA) | Phase-2       | NCT01782742             |
| 6     | Bryostatin 1          | Axiom Research/Neurotrope (New York, NY, USA) | Phase-2 | NCT04538066             |
| 7     | RO4602522             | Roche (Basel, Switzerland)    | Phase-2         | NCT01677754             |
| 8     | Al-002                | Alector Inc. (South San Francisco, CA, USA) | Phase-2 | NCT04592874             |
| 9     | JNJ-54861911          | Janssen Research (New Brunswick, NJ, USA) | Phase-1       | NCT02211079             |
| 10    | PF-04360365           | Pfizer (New York, NY, USA)    | Phase-1         | NCT00733642             |
| 11    | SAM-531               | Pfizer (New York, NY, USA)    | Phase-1         | NCT00966966             |
| 12    | V950                  | Merck Sharp & Dohme Corp (Kenilworth, NJ, USA) | Phase-1 | NCT00464334             |

### 3. Cholinesterase Inhibitory Activity of Different Plant Extracts

A summary of several medicinal plants is reported in Tables 2 and 3 in alphabetical order, along with their scientific name plant part, solvent extract, percentage concentration, and inhibition zone of enzyme. For acetylcholinesterase (AChE) inhibitory activity, three Corydalis species have been tested while, in Danish folk medicine, methanol and aqueous extracts of 11 plants are used for improvement of cognition and memory [65].

Extracts of *Corydalis* species were reported to show significant dose dependent inhibitory activity, while enzymes showed only moderate inhibition against extracts of *Lavandula augustifoli* Milller, *Ruta graveolens* L., *Rosmarinus officinalis* L., *Mentha spicata* L., and *Petroselinum crispum* (Mill). The latter plant extracts comprise vital oils with a cluster of compounds called terpenes, which have AChE ceasing activity [66]. Another study from Portugal reported the AChE inhibitory activity of the ethanol extract, essential oil, and decoction of 10 plant extracts [67]. Among the plant extracts, *Melissa officinalis* and *Malva suaveolens* exhibited AChE inhibitory activity, whereas *Paromychia argentea*, *Sanguisorba minor*, *Malva silvestris*, *Hypericum undulatum*, and *Melissa officinalis* are used in herbal treatments, *Mentha suaveolens* and *Laurus nobilis* as condiments and *Lavandula pedunculata* and *Lavandula augustifolia* as aromatic treatments. Ethanolic extracts of *L. nobilis*, *H. undulatum*, and *S. minor* showed 78% (1 mg/mL), 68% (0.5 mg/mL), and 64% (1 mg/mL) of AChE inhibition activity, respectively. Meanwhile, extracts of *H. undulatum*, *M. suaveolens*, and *L. pedunculata* showed inhibition of 82%, 69%, and 68%, respectively. Figure 1 depicts the therapeutic interventions of phytochemicals and nanoparticles in the treatment of Alzheimer’s disease.

In addition, a summary of medicinal plants in Table 3 is listed along with its butyrylcholinesterase inhibitory activity, which has been revealed to be associated with the development of Alzheimer’s disorders, as it decreases the acetylcholine, a key neurotransmitter in AD and dementia. By the in vitro method of Ellman, the methanol: chloroform (1:1) extracts of 21 plants were tested for anticholinesterase activity against BChE enzyme [68]. Extracts of *Corydalis solida*, *Solida Buxus sempervirens*, and *Rhododendron ponticum* showed
inhibition at 1 mg/mL, whereas at 10 μg/mL, extracts did not show any inhibition [69]. Using a modified version of Ellman’s protocol, the crucial oils of *Origanum ehrenbergii* and *Origanum syriacum* were screened for their BChE inhibitory activity. *O. ehrebergii* showed the highest activity.

Figure 1. Therapeutic interventions of phytochemicals and nanoparticles in the treatment. (1) Beta-amyloid fragments cluster together and forms plaques. They appear to have a toxic effect on neurons and disrupt cell-to-cell communication. (2) In Alzheimer’s disease, tau proteins change shape and organize themselves into structures called neurofibrillary tangles. The tangles disrupt the transport system and are toxic to cells. (3) Nanoparticles effectively disintegrate mature fibrils and inhibit formation of the β-amyloid fibrillation. (4) Multiple phytochemicals are considered as potent anti-Alzheimer’s medications due to their inhibitory potential for key neurotransmitters in AD. (5) Problems associated with Alzheimer’s disease: Restlessness, Agitation, Depression, Bowel problems, Wandering, Dry mouth, etc.
Data from several experiments have shown that all oils with beneficial properties are used as beneficial new flavors for nutraceutical or dietary goods with a particular use to supplement the old flavors. The probable BChE inhibitory function was tested for chloroform, ethyl acetate, ethanol, and petroleum ether extracts from 14 Salvia plants. More than 90% of BChE inhibitory activity was demonstrated by the chloroform extracts of Salvia ceratophylla and Salvia candidissima, the ethyl acetate extracts of Salvia migrostegia and Salvia frigida, and the petroleum ether extract of Salvia cyanescens [68]. Out of 20 plant extracts, extracts of dry plant parts from Nardostachys jatamansi (rhizome), Nelumbo nucifera (flower), Emblica officinalis (fruits) Rauvolfia serpentina (root), Punica granatum (fruit), and Terminalia chebula (fruit) were preferred as effective sources of AChE inhibitors.

Multi targeted drugs are preferred for the treatment of AD, owing to the multifaceted pathogenesis of AD. These plants extracts are used conventionally for curing CNS abnormalities revealed in vitro AChE inhibition [70]. Another study reported the AChE inhibitory activity of various plants, including Cupressus sempervirens L., Citrus aurantium L., and Eucalyptus globulus Labill [71]. The essential oils of A. melegueta displayed a poor to moderate propensity for inhibitory AChE activity. Priority of effectiveness for extracts is measured as seed > leaf > stem > rhizome. Low efficacy of A. melegueta rhizome extract can be closely related to the simultaneous occurrence of sesquiterpenes and monoterpenes, which may enable antagonistic contact [72]. The AChE inhibitory activity is reliant on the relationship of various terpenoid substances. Numerous connections counting synergy between monoterpenes and an antagonistic relationship between sesquiterpenes and monoterpenoids have also been reported [73].

Table 2. List of Medicinal Plants and Their Traditional Uses Related to CNS [74,75].

| Botanical Name         | Family              | Common Name      | Traditional Use                        |
|------------------------|---------------------|------------------|----------------------------------------|
| Acorus calamus         | Araceae             | Sweet flag       | Insomnia, insanity, neuropathy         |
| Bacopa monniera        | Scrophulariaceae    | Water hyssop     | Epilepsy, insanity, memory loss        |
| Cedrus deodora         | Pinaceae            | Deoder, Cedar    | Insanity                               |
| Celastrus paniculatus  | Celastraceae        | Black oil tree   | Anxiety, epilepsy                      |
| Centella asiatica      | Apiaceae            | Indian pennywort | Insomnia, mental retardation           |
| Convolvulus pluricaulis| Convolvulaceae      | Bindweed         | To improve memory and intellect        |
| Coriandrum sativum     | Umbelliferae        | Coriander        | Anti-aging                             |
| Emblica officinalis    | Euphorbiaceae       | Gooseberry       | To improve vitality and memory         |
| Evolvulus alsinoides   | Convolvulaceae      | Dwarf morning glory | To improve memory                      |
| Glicyrrhiza glabra     | Leguminosae         | Licorice         | To enhance memory                      |
| Nardostachys jatamansi | Valerianaceae       | Indian spikenard | Insanity, epilepsy, insomnia           |
| Nelumbo nucifera       | Nelumbonaceae       | Lotus            | Insomnia, restlessness                 |
| Punica granatum        | Puniceae            | Pomegranate      | Anti-aging                             |
| Rauwolfia serpentina   | Apocynaceae         | Snakeroot        | Insanity, epilepsy                     |
| Saussarea lappa        | Asteraceae          | Costus           | To treat neuropathy                    |
| Terminalia chebula     | Combretaceae        | Chebulic myrobalan | General debility                      |
| Tinospora cordifolia   | Menispermacaeae     | Tinospora        | Anti-aging                             |
| Trigonella foetens     | Fabaceae            | Fenugreek        | Anti-diabetic                          |
| Valeriana wallchicci   | Valerianaceae       | Indian Valerian  | Emotional stress                       |
| Withania somminifera   | Solanaceae          | Winter cherry    | Rejuvenating nerve tonic               |
| Botanical Name                | Part Used       | Type of Extract | AChE Inhibition and Concentration Used                  | BChE Inhibition and Concentration Used                  | Reference |
|------------------------------|-----------------|-----------------|--------------------------------------------------------|--------------------------------------------------------|-----------|
| *Acanthus ebracteatus*       | Aerial part     | Methanol        | TLC and 96 well plate; 36.19 ± 8.00 (0.1 mg/mL)        | ND                                                     | [76]      |
| *Andrographis paniculata*    | Aerial part     | Hydroalcohol    | 96 well plate; 50% (222.41 µg/mL)                      | ND                                                     | [77]      |
| *Acorus calamus* L.          | Rhizomes        | Methanol        | 96 well plate; 50% (791.35 µg/L)                       | ND                                                     | [78]      |
| *Buxux sempervirens* L.      | Whole plant     | Chloroform Methanol (1:1) | 96 well plate; 61.76 ± 0.76 (1 mg/mL) | ND                                                     | [79]      |
| *Carum carvi* L.             | Radix           | Methanol        | TLC and 96 well plate; 11.00 ± 0.90 (0.1 mg/mL)        | ND                                                     | [80]      |
| *Carthamus tinctorius* L.    | Flower          | Methanol        | TLC and 96 well plate; 30.33 ± 9.22 (0.1 mg/mL)        | ND                                                     | [76]      |
| *Capsella bursa-pastoris* L. | Whole plant     | Methanol        | 96 well plate; 10.00 ± 2.00 (5 mg/mL)                  | 96 well plate; 13.00 ± 1.00 (5 mg/mL)                 | [81]      |
| *Dioscorea bulbifera* L.     | Whole plant     | Methanol        | 96 well plate; 79.00 ± 2.00 (5 mg/mL)                  | 96 well plate; 82.00 ± 2.00 (5 mg/mL)                 | [81]      |
| *Euonymus sachalinensis*     | Leaf            | Methanol        | 96 well plate; 10.00 ± 3.00 (5 mg/mL)                  | 96 well plate; 43.00 ± 1.00 (5 mg/mL)                 | [81]      |
| *Euphorbia antiquorum* L.    | Stem            | Methanol        | TLC and 96 well plate; 42.31 ± 9.10 (0.1 mg/mL)        | ND                                                     | [76]      |
| *Hypericum undulatum*        | Flower          | Water           | UV spectrometry; 81.70 ± 3.40 (5 mg/mL)                | ND                                                     | [67]      |
| *Lycopodium clavatum* L.     | Whole plant     | Chloroform Methanol (1:1) | 96 well plate; 49.85 ± 31.33 (1 mg/mL) | ND                                                     | [79]      |
| *Michelia champaca* L.       | Leaf            | Methanol        | TLC and 96 well plate; 38.88 ± 4.56 (0.1 mg/mL)        | ND                                                     | [82]      |
| *Magnifera indica* L.        | Bark            | Methanol        | TLC and 96 well plate; 8.15 ± 0.77 (100 µg/mL)         | ND                                                     | [83]      |
Table 3. Cont.

| Botanical Name               | Part Used  | Type of Extract | AChE Inhibition and Concentration Used | BChE Inhibition and Concentration Used | Reference |
|------------------------------|------------|-----------------|---------------------------------------|----------------------------------------|-----------|
| *Pimpinella anisum* L.       | Fruit      | Methanol        | TLC and 96 well plate; 3.00 ± 0.10 (0.1 mg/mL) | ND                                     | [66]      |
| *Paronychia argentea* Lam.   | Aerial parts | Water        | UV spectrometry; 26.10 ± 0.82 (5 mg/mL) | ND                                     | [67]      |
| *Robinia pseudoacaca* L.     | Whole plant | Chloroform Methanol (1:1) | 96 well plate; 26.32 ± 0.82 (1 mg/mL) | 96 well plate; 31.47 ± 0.99 (1 mg/mL) | [79]      |
| *Rhodiola resea* L.          | Root       | Methanol        | 96 well plate; 26.32 ± 0.82 (1 mg/mL) | 96 well plate; 31.47 ± 0.99 (1 mg/mL) | [79]      |
| *Symplocos chinesis*         | Whole plant | Methanol        | 96 well plate; 74.00 ± 2.00 (5 mg/mL) | 96 well plate; 75.00 ± 2.00 (5 mg/mL) | [81]      |
| *Semecarpus anacardium* Linn.| Bark       | Methanol        | TLC and 96 well plate; 69.94 ± 0.75 (100 µg/mL) | ND                                     | [83]      |
| *Terminalia bellirica*       | Fruit      | Methanol        | TLC and 96 well plate; 39.68 ± 8.15 (0.1 mg/mL) | ND                                     | [76]      |
| *Terminalia chebula*         | Fruit      | Methanol        | 96 well plate; 89.00 ± 1.00 (5 mg/mL) | 96 well plate; 95.00 ± 1.00 (5 mg/mL) | [76]      |
| *Withania somnifera* Dunal.  | Root       | Methanol        | TLC and 96 well plate; 75.95 ± 0.16 (100 µg/mL) | ND                                     | [83]      |
4. Biogenic Metal Nanoparticles for Treatment of Alzheimer’s Disease

The drugs/molecules delivery into the brain vasculature is a tough job and if made successful, it may in turn facilitate the handling of neural disorders. The brain blood barrier (BBB) system interlinks the neural tissue with circulating blood. BBB is responsible for regulating brain homeostasis, as well as maintaining ion and molecule movement. Cessation of this dedicated multicellular structure causes neurodegeneration and neuroinflammation. In several neurotic disorders such as Parkinson’s, stroke, and Alzheimer’s, the BBB has been found to be impaired. Most of the drug candidates intended for the therapy of AD cannot pass on the barricade imposed by BBB.

The therapeutic treatments of Alzheimer’s disorder mainly target the metal chelation, aggregation of β-Amyloid (βA), inhibition of inflammation, and neurotransmitter modulation. The most suitable approach for treatment of AD is targeting (βA). In a latest study, monoclonal antibody functionalized PEGylated nanoparticles (NP5) has been fixed towards (βA), which displays improved results in the rebuilding of memory followed by clearing (βA), as well as binding results in mice [85]. In another study, it was verified that the PEGylated NP5 in the systematic circulation adsorb the lethal βA, which can improve the situation [86].

Metal-based nanoparticles (MNPS) are used for different applications, but more study is needed to use them for AD. After MNPS administration, absorption takes place in organs and appears in other tissues, such as the cortex. The brain appears to be the most susceptible organ and may be provoked by the accretion of certain metals, contributing to neurotoxicity [87]. In certain research, oxidative stress is one of the key triggers of AD expansion and neurotoxicity is caused by metals. Neural cells tested with antioxidants along with MNPS, such as TiO2, ZnO, and Ag, have demonstrated decreased metal-based neurotoxicity by reducing ROS in many study trials. MNPS translocated and deposited in the brain, where they can cause everlasting injury. Due to being less antioxidant and having less toxic selenium, NP5 have fascinated numerous researchers.

The presence of Selenium NPs in the body in AD is known to have a neuroprotective effect that can increase oxidative stress. A B6 peptide coated with sialic acid selenium NPs shows effective results in crossing BBB in recent tests. In view of converging findings, metal-based neurotoxicity remains distant and further research is needed [88]. In a recent study, a medicinal plant Terminalia arjuna, known in folklore as a medicine for varied health effects, was used for the biogenic synthesis of gold NPs. The manufactured gold NPs were not only active for disrupting mature fibrils but were also used in deterring the fibrillation process of βA, as well as being effective in ChE inhibiting activity. The inhibition of ChE is a widespread approach to improve the AD condition by enhancing acetylcholine content. T. arjuna refereed gold NPs in zebra fish were found to be non-hazardous and biocompatible [17].

In addition to being used in the biosynthesis of NPs, medicinal plants also provide coveted chemical compounds that can be used as soothing agents for the cure of AD. There are numerous detrimental factors (cost and toxicity) linked with the physicochemical synthesis method of NPs, which may hinder their usage as operative nanomedicines [89]. It is worth noting that the chemical compounds in chemical synthesis remain bound to the surface of NPs, causing potential toxicity [90].

Hence a novel method of synthesizing green NPs emerged in which medicinal plants or pure phytochemicals are used for maintenance and chelation of biocompatible NPs [91]. Epigallocatechin gallate (EGCG) functionalized selenium NPs, an important neuroprotective agent, has been used for AD therapy. The polyphenol EGCG can inhibit several amyloid-developing proteins (transthyretin, huntingtin, and alpha-synuclein) that are involved in the production of AD. In addition, EGCG and other polyphenols can also be used as effective agents for AD treatment [92].

A previous study reported by Khalil et Al. in 2019 showed inhibition of several metallic NPs against AChE and BChE enzymes. The biogenic metal oxide nanoparticles were tested at concentrations ranging from 1000 mg/mL to 62.5 mg/mL. Impressively,
the response of both enzymes to inhibition was shown to be dosage dependent. Biogenic lead oxide (PbO) nanoparticles were among the highly active samples, inhibiting the cholinesterases by 71% (AChE) and 67% (BChE) at 1000 mg/mL. This was followed by cobalt oxide nanoparticles, which showed a 70% and 68% suppression of AChE and BChE, respectively. The biogenic iron oxide nanoparticles were the least effective, with IC50 values of 160.81 mg/mL and 261.67 mg/mL for AChE and BChE, respectively.

The brain blood barrier (BBB) is one of the most difficult barriers to overcome in the treatment of Alzheimer's disease; despite this, nanoscaled materials can carry medications across the BBB. By connecting metal oxide NPs, they can be employed as delivery vehicles with potential drugs for the treatment of Alzheimer's disease. To improve biocompatibility, these metal oxides can be coated with biocompatible polymers. To reap the benefits of using metal oxide nanoparticles for Alzheimer's disease, extensive study is necessary, with a focus on the safety and efficacy of metal oxide nanoparticles. This is an open field of study. The safety of metal or metal oxide nanoparticles, such as lead oxide, is a source of concern. Further study that considers the safety concerns is advised in light of the above literature.

5. Conclusions and Future Prospects

The aforementioned attempts aimed to treat Alzheimer's disease, Parkinson's disease, senile, ataxia, dementia, gravis, and myasthenia. They also focused on reducing the cholinergic discrepancy through the use of BChE and AChE inhibitors. Many medicines, including plant-derived alkaloid galanthamine, are on the market. However, as seen in this report, a quest for more influential agents with less disadvantages has led to many medicinal plants being tested for future intervention. Phytotherapeutics and nanomedicines dominate current and potential research areas for the controlled delivery of drugs. In AD treatment, a significant number of phytochemicals have shown considerable efficacy. The effectiveness of these phytochemicals can be improved by using nanotechnology-based natural products to deliver drugs more efficiently to the target site. In addition, the in vivo activity of active compounds and nano-oxides in animal models and in human subjects must be tested in order to assess their effectiveness in the metabolic system. Such upcoming studies would be important to develop a standing and restricted therapeutic repertoire for most neural diseases, in particular affecting side-effect remedies that restrict their efficacy.

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