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

Roby Gul [1], Hasnain Jan [2,*], Gul Lalay [3], Anisa Andleeb [2], Hazrat Usman [2], Rimsha Zainab [4], Zeeshan Qamar [5], Christophe Hano [6] and Bilal Haider Abbasi [2,*]

1   Institute of Biotechnology and Genetic Engineering, Agriculture University Peshawar, Peshawar 25120, Pakistan; robiikhan112@gmail.com
2   Department of Biotechnology, Quaid-i-Azam University, Islamabad 45329, Pakistan; ansaandleeb097@gmail.com (A.A.); usmanhazrat888@gmail.com (H.U.)
3   Department of Botany, University of Peshawar, Peshawar 25120, Pakistan; gullalay573@gmail.com
4   Department of Botany, Women University of Swabi, Swabi 94640, Pakistan; mishikn@yahoo.com
5   Department of Biotechnology and Genetic Engineering, University of Hazara, Mansehra 21120, Pakistan; zeeshanqamar861@gmail.com
6   Laboratoire de Biologie des Ligneux et des Grandes Cultures, University of Orleans, (LBLGC), INRAE SC1328, F28000 Chartres, France; hano@univ-orleans.fr
*   Correspondence: rhasnain849@gmail.com (H.J.); bhabbasi@qau.edu.pk (B.H.A.); Tel.: +92-305-8464348 (H.J.); +92-77-698-41-48 (B.H.A.)

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.

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 plates, 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 neuropharmacological 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 neurode-generation 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 donepezile, 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 *Lavandaula 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 *Paronychia 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 butyrlcholinesterase 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 semperivirens,* 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 ehrenbergi* and *Origanum syriacum* were screened for their BChE inhibitory activity. *O. ehrebergii* showed the highest activity.
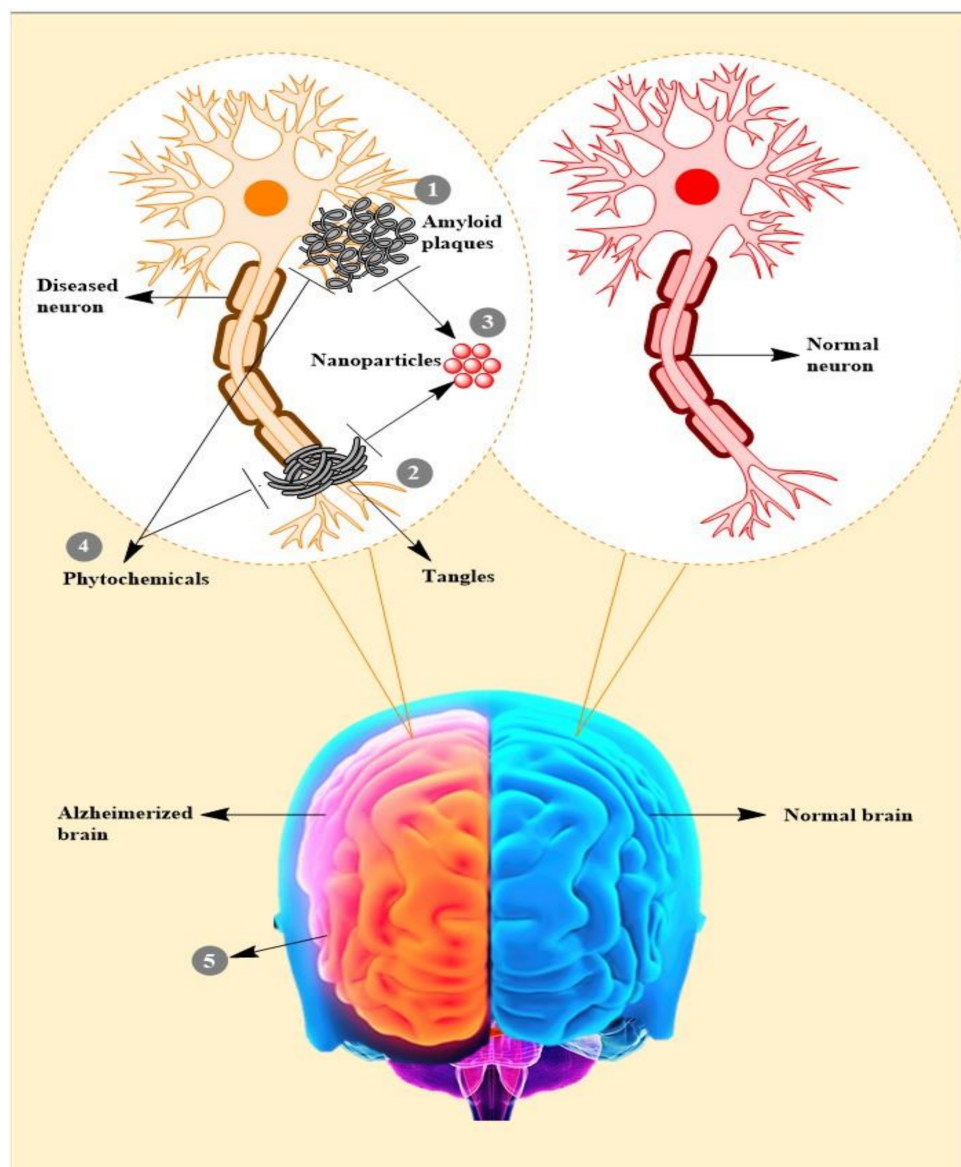

Figure 1. Therapeutic interventions of phytochemicals and nanoparticles in the treatment. (1) Beta-amyloid fragments cluster together and forms plaques. They appear to have a toxic effect on neurons and disrupt cell-to-cell communication. (2) In Alzheimer's disease, tau proteins change shape and organize 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 serpentine* (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 sesquiterepenes 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 deodera	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 enhance memory and intellect
Coriandum sativum	Umbelliferae	Coriander	To improve vitality and memory
Emblica officinalis	Euphorbiaceae	Gooseberry	Anti-aging
Evolvulus alsinoides	Convolvulaceae	Dwarf morning glory	To improve memory
Glycyrrhiza glabra	Leguminosae	Licorice	To enhance memory
Nardostachys jatamansi	Valerianaceae	Indian spikenard	Insanity, epilepsy, insomnia
Nelumbo nucifera	Nelumbonaceae	Lotus	Insomnia, restlessness
Punica granatum	Punicaceae	Pomegranate	Anti-aging
Rauvolfia serpentina	Apocynaceae	Snakeroot	Insanity, epilepsy
Saussurea lappa	Asteraceae	Costus	To treat neuropathy
Terminalia chebula	Combretaceae	Chebulic myrobalan	General debility
Tinospora cordifolia	Menispermaceae	Tinospora	Anti-aging
Trigonella foenum	Fabaceae	Fenugreek	Anti-diabetic
Valeriana wallichii	Valerianaceae	Indian Valerian	Emotional stress
Withania somminifera	Solanaceae	Winter cherry	Rejuvenating nervine tonic

Table 3. Cholinesterase Inhibitory Activity of Different Plant Extracts.

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 μmg/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; 42.00 ± 3.20 (10 g/mL)	ND	[84]
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 (NP$_S$) 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 NP$_S$ 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 TiO_2, 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, NP$_S$ 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.

Author Contributions: Conceptualization, R.G. and H.J.; software, A.A. and Z.Q.; validation, H.J. and B.H.A.; formal analysis, G.L.; writing—original draft preparation, H.J.; writing—review and editing, H.J. and C.H.; visualization, H.U. and R.Z.; supervision, C.H and B.H.A.; All authors have read and agreed to the published version of the manuscript.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Akter, R.; Rahman, H.; Behl, T.; Chowdhury, M.; Rahman, A.; Manirujjaman, M.; Bulbul, I.J.; Elshenaw, S.E.; Tit, D.M.; Bungau, S. Prospective role of polyphenolic compounds in the treatment of neurodegenerative diseases. *CNS Neurol. Disord. Drug Targets* **2020**, *20*. [CrossRef]
2. Bredesen, D.; Sharlin, K.; Jenkins, D.; Okuno, M.; Youngberg, W.; Cohen, S.; Stefani, A.; Brown, R.; Conger, S.; Tanio, C. Reversal of cognitive decline: 100 patients. *J. Alzheimer's Dis. Parkinsonism* **2018**, *8*. [CrossRef]
3. Budson, A.E.; Solomon, P.R. *Memory Loss, Alzheimer's Disease, and Dementia: A Practical Guide for Clinicians*; Elsevier Health Sciences: Amsterdam, The Netherlands, 2015.
4. Mullane, K.; Williams, M. Alzheimer's disease (AD) therapeutics–2: Beyond amyloid–re-defining AD and its causality to discover effective therapeutics. *Biochem. Pharmacol.* **2018**, *158*, 376–401. [CrossRef] [PubMed]

5. Hampel, H.; Mesulam, M.-M.; Cuello, A.C.; Khachaturian, A.S.; Vergallo, A.; Farlow, M.; Snyder, P.; Giacobini, E.; Khachaturian, Z. Revisiting the cholinergic hypothesis in Alzheimer's disease: Emerging evidence from translational and clinical research. *J. Prev. Alzheimer's Dis.* **2019**, *6*, 2–15. [CrossRef]

6. Mughal, E.U.; Javid, A.; Sadiq, A.; Murtaza, S.; Zafar, M.N.; Khan, B.A.; Sumrra, S.H.; Tahir, M.N.; Khan, K.M. Synthesis, structure-activity relationship and molecular docking studies of 3-O-flavonol glycosides as cholinesterase inhibitors. *Bioorg. Med. Chem.* **2018**, *26*, 3696–3706. [CrossRef]

7. Cao, T.Q.; Ngo, Q.-M.T.; Seong, S.H.; Youn, U.J.; Kim, J.A.; Kim, J.; Kim, J.-C.; Woo, M.H.; Choi, J.S.; Min, B.S. Cholinesterase inhibitory alkaloids from the rhizomes of Coptis chinensis. *Bioorg. Chem.* **2018**, *77*, 625–632. [CrossRef] [PubMed]

8. Rafii, M.S.; Aisen, P.S. Advances in Alzheimer's disease drug development. *BMC Med.* **2015**, *13*, 4. [CrossRef]

9. Firdaus, Z.; Singh, T.D. An insight in pathophysiological mechanism of Alzheimer's disease and its management using plant natural products. *Mini Rev. Med. Chem.* **2021**, *21*, 35–57. [CrossRef]

10. Hodges, J.R. Alzheimer's centennial legacy: Origins, landmarks and the current status of knowledge concerning cognitive aspects. *Brain* **2006**, *129*, 2811–2822. [CrossRef] [PubMed]

11. Sharma, K. Cholinesterase inhibitors as Alzheimer's therapeutics. *Mol. Med. Rep.* **2019**, *20*, 1479–1487. [CrossRef]

12. Kabir, M.T.; Uddin, M.; Begum, M.; Thangapandiyan, S.; Rahman, M.; Aleya, L.; Mathew, B.; Ahmed, M.; Barreto, G.E.; Ashraf, G.M. Cholinesterase inhibitors for Alzheimer's disease: Multitargeting strategy based on anti-Alzheimer's drugs repositioning. *Curr. Pharm. Des.* **2019**, *25*, 3519–3535. [CrossRef] [PubMed]

13. Zaki, A.G.; El-Sayed, E.-S.R.; Abd Elkodous, M.; El-Sayyad, G.S. Microbial acetylcholinesterase inhibitors for Alzheimer's therapy: Recent trends on extraction, detection, irradiation-assisted production improvement and nano-structured drug delivery. *Appl. Microbiol. Biotechnol.* **2020**, *104*, 4717–4735. [CrossRef] [PubMed]

14. Khan, A.; Jahan, S.; Alshahrani, S.; Alshehri, B.M.; Sameer, A.S.; Arafah, A.; Ahmad, A.; Rehman, M.U. Phytotherapeutic agents for neurodegenerative disorders: A neuropharmacological review. In *Phytomedicine*; Elsevier: Amsterdam, The Netherlands, 2021; pp. 581–620.

15. Taki, M.; Hasegawa, T.; Ninoyu, Y.; Hirano, S. Efficacy of Yokukansan, a traditional Japanese herbal medicine, in patients with dizziness and irritability. *Auris Nasus Larynx* **2021**. [CrossRef]

16. Tewari, D.; Joshi, T.; Sah, A.N. Galanthus nivalis L. (snowdrop). In *Naturally Occurring Chemicals Against Alzheimer's Disease*; Elsevier: Amsterdam, The Netherlands, 2021; pp. 301–315.

17. Suganthy, N.; Ramkumar, V.S.; Pugazhendhi, A.; Benelli, G.; Archunan, G. Biogenic synthesis of gold nanoparticles from Terminalia arjuna bark extract: Assessment of safety aspects and neuroprotective potential via antioxidant, anticholinesterase, and antiamyloidogenic effects. *Environ. Sci. Pollut. Res.* **2018**, *25*, 10418–10433. [CrossRef]

18. Mandal, S.; Debnath, K.; Jana, N.R.; Jana, N.R. Trehalose-functionalized gold nanoparticle for inhibiting intracellular protein aggregation. *Langmuir* **2017**, *33*, 13996–14003. [CrossRef] [PubMed]

19. Nellore, J.; Pauline, C.; Amarnath, K. Bacopa monnieri phytochemicals mediated synthesis of platinum nanoparticles and its neurorescue effect on 1-methyl 4-phenyl 1, 2, 3, 6 tetrahydropyridine-induced experimental parkinsonism in zebrafish. *J. Neurodegener. Dis.* **2013**, *2013*. [CrossRef]

20. Nazıroğlu, M.; Muhamad, S.; Pecze, L. Nanoparticles as potential clinical therapeutic agents in Alzheimer's disease: Focus on selenium nanoparticles. *Exp. Rev. Clin. Pharmacol.* **2017**, *10*, 773–782. [CrossRef]

21. Grundy, E.M.; Murphy, M. Population ageing in Europe. *Oxf. Textb. Geriatr. Med.* **2017**, *11*. [CrossRef]

22. WHO. *Risk Reduction of Cognitive Decline and Dementia*; WHO Guidelines; WHO: Geneva, Switzerland, 2019.

23. Solfrizzi, V.; Scafato, E.; Lozupone, M.; Seripa, D.; Schilardi, A.; Custodero, C.; Sardone, R.; Galluzzo, L.; Gandin, C.; Baldereschi, M. Biopsychosocial frailty and the risk of incident dementia: The Italian longitudinal study on aging. *Alzheimer's Dement.* **2019**, *15*, 1019–1028. [CrossRef]

24. Trevisan, K.; Cristina-Pereira, R.; Silva-Amaral, D.; Aversi-Ferreira, T.A. Theories of aging and the prevalence of Alzheimer's disease. *BioMed Res. Int.* **2019**, *2019*. [CrossRef]

25. Alzheimer's Association. Alzheimer's disease facts and figures. *Alzheimer's Dement.* **2017**, *13*, 325–373. [CrossRef]

26. Qiu, C.; Fratiglioni, L. Epidemiology of Alzheimer's. In *Alzheimer's Disease*; Oxford University Press: New York, NY, USA, 2017.

27. Lobo, A.; Launer, L.; Fratiglioni, L.; Andersen, K.; Di Carlo, A.; Breteler, M.; Copeland, J.; Dartigues, J.; Jagger, C.; Martinez-Lage, J. Prevalence of dementia and major subtypes in Europe: A collaborative study of population-based cohorts. *Neurology* **2000**, *54*.

28. Kawas, C.; Gray, S.; Brookmeyer, R.; Fozard, J.; Zonderman, A. Age-specific incidence rates of Alzheimer's disease: The Baltimore longitudinal study of aging. *Neurology* **2000**, *54*, 2072–2077. [CrossRef]

29. Jorm, A.F.; Jolley, D. The incidence of dementia: A meta-analysis. *Neurology* **1998**, *51*, 728–733. [CrossRef]

30. Miech, R.; Breitner, J.C.; Zandi, P.P.; Khachaturian, A.; Anthony, J.; Mayer, L. Incidence of AD may decline in the early 90s for men, later for women: The Cache county study. *Neurology* **2002**, *58*, 209–218. [CrossRef]

31. Qiu, C.; Kivipelto, M.; von Strauss, E. Epidemiology of Alzheimer's disease: Occurrence, determinants, and strategies toward intervention. *Dialog. Clin. Neurosci.* **2009**, *11*, 111.

32. Chandra, V.; Pandav, R.; Dodge, H.; Johnston, J.; Belle, S.; DeKosky, S.; Ganguli, M. Incidence of Alzheimer's disease in a rural community in India: The Indo–US study. *Neurology* **2001**, *57*, 985–989. [CrossRef]

33. Kalaria, R.N.; Maestre, G.E.; Arizaga, R.; Friedland, R.P.; Galasko, D.; Hall, K.; Luchsinger, J.A.; Ogunniyi, A.; Perry, E.K.; Potocnik, F. Alzheimer's disease and vascular dementia in developing countries: Prevalence, management, and risk factors. *Lancet Neurol.* **2008**, *7*, 812–826. [CrossRef]

34. Kivipelto, M.; Mangialasche, F.; Ngandu, T. Lifestyle interventions to prevent cognitive impairment, dementia and Alzheimer disease. *Nat. Rev. Neurol.* **2018**, *14*, 653–666. [CrossRef]

35. Larsson, S.C.; Traylor, M.; Malik, R.; Dichgans, M.; Burgess, S.; Markus, H.S. Modifiable pathways in Alzheimer's disease: Mendelian randomisation analysis. *BMJ* **2017**, *359*, 5375. [CrossRef]

36. Yuan, H.; Yang, W. Genetically determined serum uric acid and Alzheimer's disease risk. *J. Alzheimer's Dis.* **2018**, *65*, 1259–1265. [CrossRef]

37. Rajabli, F.; Feliciano, B.E.; Celis, K.; Hamilton-Nelson, K.L.; Whitehead, P.L.; Adams, L.D.; Bussies, P.L.; Manrique, C.P.; Rodriguez, A.; Rodriguez, V. Ancestral origin of ApoE ε4 Alzheimer disease risk in Puerto Rican and African American populations. *PLoS Gen.* **2018**, *14*, e1007791. [CrossRef] [PubMed]

38. Wajman, J.R.; Mansur, L.L.; Yassuda, M.S. Lifestyle patterns as a modifiable risk factor for late-life cognitive decline: A narrative review regarding dementia prevention. *Curr. Aging Sci.* **2018**, *11*, 90–99. [CrossRef]

39. Vemuri, P.; Lesnick, T.G.; Przybelski, S.A.; Knopman, D.S.; Lowe, V.J.; Graff-Radford, J.; Roberts, R.O.; Mielke, M.M.; Machulda, M.M.; Petersen, R.C. Age, vascular health, and Alzheimer disease biomarkers in an elderly sample. *Ann. Neurol.* **2017**, *82*, 706–718. [CrossRef]

40. Ricci, M.; Chiaravalloti, A.; Martorana, A.; Koch, G.; Barbagallo, G.; Schillaci, O. The role of epsilon phenotype in brain glucose consumption in Alzheimer's disease. *Ann. Nucl. Med.* **2020**, *34*, 254–262. [CrossRef]

41. Matloff, W.J.; Zhao, L.; Ning, K.; Conti, D.V.; Toga, A.W. Interaction effect of alcohol consumption and Alzheimer disease polygenic risk score on the brain cortical thickness of cognitively normal subjects. *Alcohol* **2020**, *85*, 1–12. [CrossRef]

42. Topiwala, A.; Ebmeier, K.P. Effects of drinking on late-life brain and cognition. *Evid. Based Ment. Health* **2018**, *21*, 12–15. [CrossRef] [PubMed]

43. Power, M.C.; Rawlings, A.; Sharrett, A.R.; Bandeen-Roche, K.; Coresh, J.; Ballantyne, C.M.; Pokharel, Y.; Michos, E.D.; Penman, A.; Alonso, A. Association of midlife lipids with 20-year cognitive change: A cohort study. *Alzheimer's Dement.* **2018**, *14*, 167–177. [CrossRef]

44. Anstey, K.J.; Ashby-Mitchell, K.; Peters, R. Updating the evidence on the association between serum cholesterol and risk of late-life dementia: Review and meta-analysis. *J. Alzheimer's Dis.* **2017**, *56*, 215–228. [CrossRef]

45. Svensson, T.; Sawada, N.; Mimura, M.; Nozaki, S.; Shikimoto, R.; Tsugane, S. The association between midlife serum high-density lipoprotein and mild cognitive impairment and dementia after 19 years of follow-up. *Transl. Psychiatry* **2019**, *9*, 1–9. [CrossRef] [PubMed]

46. Davis, K.A.; Bishara, D.; Perera, G.; Molokhia, M.; Rajendran, L.; Stewart, R.J. Benefits and harms of statins in people with dementia: A systematic review and meta-analysis. *J. Am. Geriatr. Soc.* **2020**, *68*, 650–658. [CrossRef]

47. Bunt, C.W.; Hogan, A.J. The effect of statins on dementia and cognitive decline. *Am. Fam. Physician* **2017**, *95*, 151–152.

48. Stockwell-Smith, G.; Moyle, W.; Kellett, U. The impact of early psychosocial intervention on self-efficacy of care recipient/carer dyads living with early-stage dementia—A mixed-methods study. *J. Adv. Nurs.* **2018**, *74*, 2167–2180. [CrossRef]

49. Rusmaully, J.; Dugravot, A.; Moatti, J.-P.; Marmot, M.G.; Elbaz, A.; Kivimaki, M.; Sabia, S.; Singh-Manoux, A. Contribution of cognitive performance and cognitive decline to associations between socioeconomic factors and dementia: A cohort study. *PLoS Med.* **2017**, *14*, e1002334. [CrossRef] [PubMed]

50. Paillard, T.; Rolland, Y.; de Souto Barreto, P. Protective effects of physical exercise in Alzheimer's disease and Parkinson's disease: A narrative review. *J. Clin. Neurol.* **2015**, *11*, 212. [CrossRef]

51. Lauretta, G.; Ravalli, S.; Maugeri, G.; D'Agata, V.; Di Rosa, M.; Musumeci, G. The Impact of physical exercise on the hippocampus in physiological condition and ageing-related decline: Current evidence from animal and human studies. *Curr. Pharm. Biotechnol.* **2021**, *22*. [CrossRef]

52. Lillo-Crespo, M.; Forner-Ruiz, M.; Riquelme-Galindo, J.; Ruiz-Fernández, D.; García-Sanjuan, S. Chess practice as a protective factor in dementia. *Int. J. Environ. Res. Public Health* **2019**, *16*, 2116. [CrossRef]

53. Lafta, H.; AlMayaly, I. Potential effect of several heavy metals with Alzheimer's disease infection. *Ann. Rom. Soc. Cell Biol.* **2021**, *25*, 3476–3484.

54. Zhang, X.-Q.; Li, L.; Huo, J.-T.; Cheng, M.; Li, L.-H. Effects of repetitive transcranial magnetic stimulation on cognitive function and cholinergic activity in the rat hippocampus after vascular dementia. *Neural Regen. Res.* **2018**, *13*, 1384. [CrossRef] [PubMed]

55. Schmidt, R.; Schmidt, H.; Curb, J.D.; Masaki, K.; White, L.R.; Launer, L.J. Early inflammation and dementia: A 25-year follow-up of the Honolulu-Asia Aging Study. *Ann. Neurol.* **2002**, *52*, 168–174. [CrossRef]

56. Szekely, C.A.; Breitner, J.C.; Fitzpatrick, A.L.; Rea, T.D.; Psaty, B.M.; Kuller, L.H.; Zandi, P.P. NSAID use and dementia risk in the Cardiovascular Health Study*: Role of APOE and NSAID type. *Neurology* **2008**, *70*, 17–24. [CrossRef]

57. Arvanitakis, Z.; Grodstein, F.; Bienias, J.; Schneider, J.; Wilson, R.; Kelly, J.; Evans, D.; Bennett, D. Relation of NSAIDs to incident AD, change in cognitive function, and AD pathology. *Neurology* **2008**, *70*, 2219–2225. [CrossRef]

58. Fleminger, S.; Oliver, D.; Lovestone, S.; Rabe-Hesketh, S.; Giora, A. Head injury as a risk factor for Alzheimer's disease: The evidence 10 years on; a partial replication. *J. Neurol. Neurosurg. Psychiatry* **2003**, *74*, 857–862. [CrossRef] [PubMed]

59. Mehta, K.; Ott, A.; Kalmijn, S.; Slooter, A.; Van Duijn, C.; Hofman, A.; Breteler, M. Head trauma and risk of dementia and Alzheimer's disease: The Rotterdam Study. *Neurology* **1999**, *53*, 1959. [CrossRef] [PubMed]

60. Dal Forno, G.; Palermo, M.T.; Donohue, J.E.; Karagiozis, H.; Zonderman, A.B.; Kawas, C.H. Depressive symptoms, sex, and risk for Alzheimer's disease. *Ann. Neurol.* **2005**, *57*, 381–387. [CrossRef]

61. Sadiq, A.; Zeb, A.; Ullah, F.; Ahmad, S.; Ayaz, M.; Rashid, U.; Muhammad, N. Chemical characterization, analgesic, antioxidant, and anticholinesterase potentials of essential oils from Isodon rugosus Wall. ex. Benth. *Front. Pharmacol.* **2018**, *9*, 623. [CrossRef] [PubMed]

62. Ali, M.; Muhammad, S.; Shah, M.R.; Khan, A.; Rashid, U.; Farooq, U.; Ullah, F.; Sadiq, A.; Ayaz, M.; Ali, M. Neurologically potent molecules from Crataegus oxyacantha; isolation, anticholinesterase inhibition, and molecular docking. *Front. Pharmacol.* **2017**, *8*, 327. [CrossRef]

63. Zohra, T.; Ovais, M.; Khalil, A.T.; Qasim, M.; Ayaz, M.; Shinwari, Z.K. Extraction optimization, total phenolic, flavonoid contents, HPLC-DAD analysis and diverse pharmacological evaluations of *Dysphania ambrosioides* (L.) *Mosyakin* & *Clemants*. *Nat. Prod. Res.* **2019**, *33*, 136–142.

64. Ayaz, M.; Ovais, M.; Ahmad, I.; Sadiq, A.; Khalil, A.T.; Ullah, F. Biosynthesized metal nanoparticles as potential Alzheimer's disease therapeutics. In *Metal Nanoparticles for Drug Delivery and Diagnostic Applications*; Elsevier: Amsterdam, The Netherlands, 2020; pp. 31–42.

65. López, V.; Martín, S.; Gómez-Serranillos, M.P.; Carretero, M.E.; Jäger, A.K.; Calvo, M.I. Neuroprotective and neurological properties of Melissa officinalis. *Neurochem. Res.* **2009**, *34*, 1955–1961. [CrossRef]

66. Adsersen, A.; Gauguin, B.; Gudiksen, L.; Jäger, A.K. Screening of plants used in Danish folk medicine to treat memory dysfunction for acetylcholinesterase inhibitory activity. *J. Ethnopharmacol.* **2006**, *104*, 418–422. [CrossRef]

67. Ferreira, A.; Proença, C.; Serralheiro, M.; Araujo, M. The in vitro screening for acetylcholinesterase inhibition and antioxidant activity of medicinal plants from Portugal. *J. Ethnopharmacol.* **2006**, *108*, 31–37. [CrossRef]

68. Orhan, I.; Kartal, M.; Naz, Q.; Ejaz, A.; Yilmaz, G.; Kan, Y.; Konuklugil, B.; Şener, B.; Choudhary, M.I. Antioxidant and anticholinesterase evaluation of selected Turkish Salvia species. *Food Chem.* **2007**, *103*, 1247–1254. [CrossRef]

69. Loizzo, M.R.; Menichini, F.; Conforti, F.; Tundis, R.; Bonesi, M.; Saab, A.M.; Statti, G.A.; de Cindio, B.; Houghton, P.J.; Menichini, F. Chemical analysis, antioxidant, antiinflammatory and anticholinesterase activities of *Origanum ehrenbergii boiss* and *Origanum syriacum* L. essential oils. *Food Chem.* **2009**, *117*, 174–180. [CrossRef]

70. Basavan, D.; Chalichem, N.S.; Kumar, M.K. Phytoconstituents and their possible mechanistic profile for Alzheimer's Disease–A literature review. *Curr. Drug Targets* **2019**, *20*, 263–291. [CrossRef]

71. Aazza, S.; Lyoussi, B.; Miguel, M.G. Antioxidant and antiacetylcholinesterase activities of some commercial essential oils and their major compounds. *Molecules* **2011**, *16*, 7672. [CrossRef] [PubMed]

72. Okeke, B.M.; Adefegha, S.A.; Oyeleye, S.I.; Oboh, G. Effects of combined crude alkaloid-rich extracts from alligator pepper (*Aframomum melegueta*) and bastered melegueta (*Aframomum danielli*) on the enzymes crucial to erectile dysfunction—In vitro. *J. Food Biochem.* **2018**, *42*, e12550. [CrossRef]

73. Yu, Z.; Wang, B.; Yang, F.; Sun, Q.; Yang, Z.; Zhu, L. Chemical compositionand anti-acetyl cholinesterase activity of flower essential oils of artemisiaannuaat different flowering stage. *IJPR* **2011**, *10*, 265.

74. Jazayeri, S.B.; Amanlou, A.; Ghanadian, N.; Pasalar, P.; Amanlou, M. A preliminary investigation of anticholinesterase activity of some Iranian medicinal plants commonly used in traditional medicine. *DARU J. Pharm. Sci.* **2014**, *22*, 1–5. [CrossRef]

75. Akram, M.; Nawaz, A. Effects of medicinal plants on Alzheimer's disease and memory deficits. *Neural Regen. Res.* **2017**, *12*, 660. [CrossRef]

76. Ingkaninan, K.; Temkitthawon, P.; Chuenchom, K.; Yuyaem, T.; Thongnoi, W. Screening for acetylcholinesterase inhibitory activity in plants used in Thai traditional rejuvenating and neurotonic remedies. *J. Ethnopharmacol.* **2003**, *89*, 261–264. [CrossRef] [PubMed]

77. Mukherjee, P.K.; Kumar, V.; Houghton, P.J. Screening of Indian medicinal plants for acetylcholinesterase inhibitory activity. *Phytotherapy Res.* **2007**, *21*, 1142–1145. [CrossRef]

78. Ahmed, F.; Chandra, J.; Urooj, A.; Rangappa, K. In vitro antioxidant and anticholinesterase activity of *Acorus calamus* and *Nardostachys jatamansi* rhizomes. *J. Pharm. Res.* **2009**, *2*, 830–883.

79. Orhan, I.; Şener, B.; Choudhary, M.; Khalid, A. Acetylcholinesterase and butyrylcholinesterase inhibitory activity of some Turkish medicinal plants. *J. Ethnopharmacol.* **2004**, *91*, 57–60. [CrossRef]

80. Zelík, P.; Lukešová, A.; Voloshko, L.N.; Štys, D.; Kopecký, J. Screening for acetylcholinesterase inhibitory activity in cyanobacteria of the genus Nostoc. *J. Enzym. Inhib. Med. Chem.* **2009**, *24*, 531–536. [CrossRef]

81. Sancheti, S.; Um, B.-H.; Seo, S.-Y. 1, 2, 3, 4, 6-penta-O-galloyl-β-D-glucose: A cholinesterase inhibitor from *Terminalia chebula*. *S. Afr. J. Bot.* **2010**, *76*, 285–288. [CrossRef]

82. Mukherjee, P.K.; Kumar, V.; Mal, M.; Houghton, P.J. Acetylcholinesterase inhibitors from plants. *Phytomedicine* **2007**, *14*, 289–300. [CrossRef]

83. Vinutha, B.; Prashanth, D.; Salma, K.; Sreeja, S.; Pratiti, D.; Padmaja, R.; Radhika, S.; Amit, A.; Venkateshwarlu, K.; Deepak, M. Screening of selected Indian medicinal plants for acetylcholinesterase inhibitory activity. *J. Ethnopharmacol.* **2007**, *109*, 359–363. [CrossRef]

84. Hillhouse, B.; Ming, D.S.; French, C.; Towers, G. Acetylcholine esterase inhibitors in *Rhodiola rosea*. *Pharm. Biol.* **2004**, *42*, 68–72. [CrossRef]

85. Carradori, D.; Balducci, C.; Re, F.; Brambilla, D.; Le Droumaguet, B.; Flores, O.; Gaudin, A.; Mura, S.; Forloni, G.; Ordoñez-Gutierrez, L. Antibody-functionalized polymer nanoparticle leading to memory recovery in Alzheimer's disease-like transgenic mouse model. *Nanomed. Nanotechnol. Biol. Med.* **2018**, *14*, 609–618. [CrossRef]

86. Brambilla, D.; Verpillot, R.; Le Droumaguet, B.; Nicolas, J.; Taverna, M.; Kóňa, J.; Lettiero, B.; Hashemi, S.H.; De Kimpe, L.; Canovi, M. PEGylated nanoparticles bind to and alter amyloid-beta peptide conformation: Toward engineering of functional nanomedicines for Alzheimer's disease. *ACS Nano* **2012**, *6*, 5897–5908. [CrossRef]

87. Feng, X.; Chen, A.; Zhang, Y.; Wang, J.; Shao, L.; Wei, L. Central nervous system toxicity of metallic nanoparticles. *Int. J. Nanomed.* **2015**, *10*, 4321.

88. Yin, T.; Yang, L.; Liu, Y.; Zhou, X.; Sun, J.; Liu, J. Sialic acid (SA)-modified selenium nanoparticles coated with a high blood–brain barrier permeability peptide-B6 peptide for potential use in Alzheimer's disease. *Acta Biomater.* **2015**, *25*, 172–183. [CrossRef] [PubMed]

89. Zohra, T.; Ovais, M.; Khalil, A.T.; Qasim, M.; Ayaz, M.; Shinwari, Z.K.; Ahmad, S.; Zahoor, M. Bio-guided profiling and HPLC-DAD finger printing of *Atriplex lasiantha boiss*. *BMC Complement. Altern. Med.* **2019**, *19*, 4161. [CrossRef] [PubMed]

90. Barabadi, H.; Ovais, M.; Shinwari, Z.K.; Saravanan, M. Anti-cancer green bionanomaterials: Present status and future prospects. *Green Chem. Lett. Rev.* **2017**, *10*, 285–314. [CrossRef]

91. Khalil, A.T.; Ayaz, M.; Ovais, M.; Wadood, A.; Ali, M.; Shinwari, Z.K.; Maaza, M. In vitro cholinesterase enzymes inhibitory potential and in silico molecular docking studies of biogenic metal oxides nanoparticles. *Inorg. Nano Met. Chem.* **2018**, *48*, 441–448. [CrossRef]

92. Zhang, J.; Zhou, X.; Yu, Q.; Yang, L.; Sun, D.; Zhou, Y.; Liu, J. Epigallocatechin-3-gallate (EGCG)-stabilized selenium nanoparticles coated with Tet-1 peptide to reduce amyloid-β aggregation and cytotoxicity. *ACS Appl. Mater. Interfaces* **2014**, *6*, 8475–8487. [CrossRef]