Plants with Anti-Alzheimer Properties

Subjects: Primary Health Care

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Alzheimer's disease (AD) is a neurological disorder in humans caused by complex pathophysiological mechanisms that lead to loss of memory and cognition, death of neurons, loss of synapses, and damage of the brain, which culminates in death.

Alzheimer's disease | medicinal plants | 'ginseng | gotu kola

1. Treatment of Alzheimer's Disease

There are already more than 55 million cases of Alzheimer's disease (AD) documented globally, and by 2050, the overall number of AD patients is expected to more than triple [1][2]. Even though it is a serious health issue proper and complete treatment is not available, treatment strategies used today concentrate on assisting patients in managing behavioural symptoms, sustaining mental function, and delaying or preventing the signs of illness. Two treatment strategies can be adopted as discussed below.

1.1. Chemical-Based Treatment

Despite the fact that AD is a public health problem, there are currently only two classes of medications that have been approved by the FDA to treat AD: cholinesterase enzyme inhibitors (naturally occurring, synthetic, and hybrid analogues), and antagonists to N-methyl D-aspartate (NMDA).

1.1.1. Cholinesterase Inhibitors

According to the cholinergic theory, a reduction in the synthesis of acetylcholine (ACh) causes AD. A reduction in acetylcholinesterase along with an increase in cholinergic levels is one therapy that enhances neuronal cell and cognitive function [3]. Acetylcholine breakdown in synapses is prevented by acetylcholinesterase inhibitors (AChEIs), leading to continuous ACh build up and cholinergic receptor activation. Another approach to treating AD may involve raising choline reuptake and, consequently, the generation of acetylcholine at presynaptic terminals. This might be done by focusing on the choline transporter (CHT1), which is in charge of supplying the choline required for the synthesis of ACh [3][4]. Different AChEIs are donepezil, rivastigmine, and galantamine.

Donepezil

The most effective medication for treating AD is donepezil, which is a derivative of indanonebenzylpiperidine and a member of the second generation of acetylcholinesterase inhibitors (AChEIs). Due to donepezil's reversible binding

to acetylcholinesterase, there is more ACh present at the synapses and prevents it from being hydrolysed. With transient cholinergic side effects that affect the neurological, as well as gastrointestinal systems, the medicine may be tolerated by the patient. Notably, donepezil is used to treat AD symptoms, such as improving cognition and behaviour [5][6]. Due to an imbalance in acetylcholine, unusual adverse reactions such as extrapyramidal side effects are more likely to occur when AD medication is used along with psychiatric medicines. A case of an extrapyramidal adverse response brought on by the donepezil and risperidone combination was reported [7]. The patient experienced fatigue, nausea, panic, sweating, and vomiting.

Rivastigmine

It is a butyrylcholinesterase (BuChE) and acetylcholinesterase (AChE) pseudo-irreversible inhibitor. In order to function, it binds to the two active sites of AChE which are estearic and anionic sites, which stops acetylcholine (Ach) metabolism [8]. In the healthy brain, glial cells contain BuChE and have only a 10% activity level compared to the AD brain, where it has a 40–90% activity level, while simultaneously reducing ACh activity. This implies that BuChE activity can be a sign of mild to severe AD. Rivastigmine is metabolised by AChE and BuChE at the synapses and dissociates slower than AChE, which is why it is known as a pseudo-irreversible. The drug is used for the treatment of mild to moderate AD. It ameliorates daily activities and cognitive processes [9][10]. The most common adverse effects of rivastigmine are gastrointestinal problems such as bladder pain, painful urination, etc.

Galantamine (GAL)

For mild to severe AD cases, it is regarded as a conventional first-line medication. Galantamine is a dual-mode selective tertiary isoquinoline alkaloid, which not only acts as a competitive inhibitor of AChE but also has the ability to allosterically bind to and activate the nicotinic acetylcholine receptors subunit. Like other AChE inhibitors, GAL has good efficacy and tolerability and can reduce behavioural symptoms and improve daily activities, cognitive performance, and mood [11][12]. For transporting the medicine only to the areas of the brain that were injured, it is linked to hydroxyapatite particles that contain ceria. To transport GAL hydrobromide, some researchers have used solid-lipid nanoparticles and nano emulsification techniques [13]. The results of these tests are promising for the safe administration of the drug. Nasal delivery of a GAL hydrobromide–chitosan combination of nanoparticles has good pharmacological potential, while the controlled release dose of the drug has been transported via the patch technique by another group. The common problems associated with this drug are gastrointestinal problems, headache, dizziness, insomnia, weight loss, loss of appetite, etc. [13][14].

1.1.2. N-methyl D-aspartate Receptor (NMDAR) Antagonists

It is thought that NMDAR performs an important role in the pathophysiology of AD. Ca^{2+} influx brought on by NMDAR activation promotes signal transduction, and results in gene transcription that is required for the growth of long-term potentiation (LTP), which is essential for the establishment of synaptic neurotransmission, plasticity, and memory [15]. Excessive NMDAR activation overstimulates glutamate, the main excitatory amino acid in the CNS, which results in excitotoxicity, synaptic malfunction, neuronal cell death, and damage to cognitive abilities. Numerous NMDAR uncompetitive antagonists have been created and tested in clinical settings, though the

majority of them were ineffective and had undesirable side effects [16]. The sole drug in this class that is approved for the treatment of moderate to severe AD is memantine.

Memantine

It is an uncompetitive, low-affinity antagonist of the glutamate receptor subtype. To treat mild to severe AD, memantine is administered alone or in combination with AChEI [12]. The drug has a low affinity and is quickly displaced from NMDAR by high quantities of glutamate. It blocks excitatory receptors without impairing regular synaptic communication, which makes it harmless, well tolerable, and avoids a long-lasting blockage. Possible adverse effects of memantine are dizziness, constipation, vomiting, hypertension, and headache [17].

1.2. Plant-Based Treatment

Currently available synthetic medicines are effective only for 1–4 years for mild to moderate AD. Synthetic medicine exhibits many negative side effects [18]. Scientific evidence related to the efficacy of phytochemicals in the prevention and treatment of AD has been accumulating which shows that they are safe and cost effective. Oxidative stress is one of the proven causes of AD. However, plants are reservoirs of antioxidants which can mitigate the effects of AD [19][20]. Several plants were examined for their ability to combat AD as listed in **Table 1** and also shown in **Figure 1**. A diet high in plants has repeatedly been linked to a lower risk of AD. It is advised to consume fruits, vegetables, cereals, and nuts on a regular basis for overall health, to promote healthy ageing, and to reduce the risk of age-related disorders such as AD [21][22].

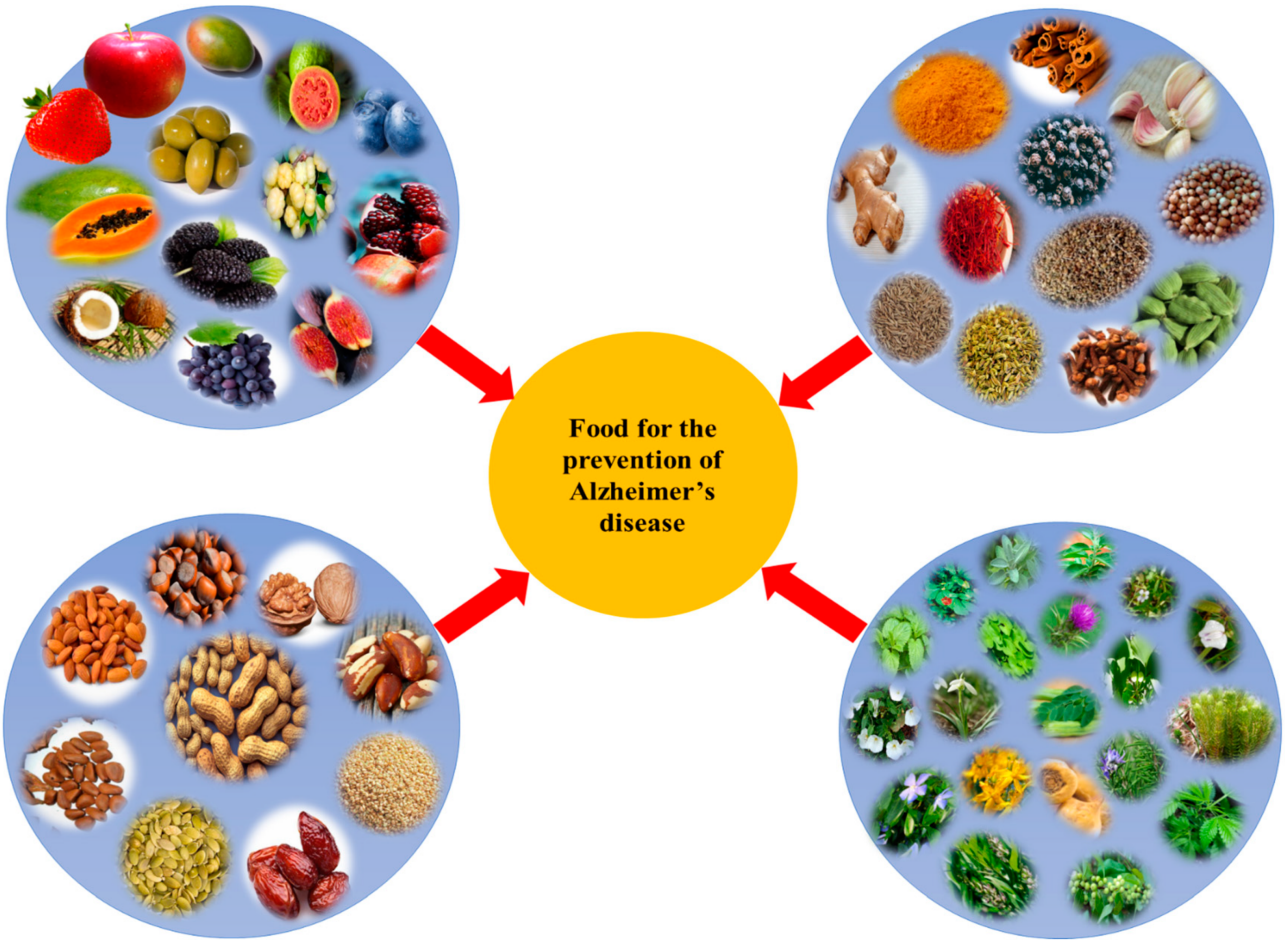

Figure 1. Different plant-based foods used for the prevention of Alzheimer's disease (AD).

Table 1. Different plants possessing anti-Alzheimer properties.

Plant	Botanical Name	Family	Part Used	Active Compounds	Properties	References
Ashwangdha	*Withania somnifera*	Solanaceae	Roots	Glycowithanolides (Withaferin A, Withasomniferin A)	It has neuroprotective functions.	[23][24]
Brahmi	*Bacopa monnieri*	Plantaginaceae	Arial parts	Brahmine, bacosides A and B, apigenin, and quercetin	It works as a memory enhancer.	[25]
Calabar bean	*Physostigma venenosum*	Fabaceae	Seeds	physostigmine	It has acetylcholinesterase inhibitor activities.	[26]
Coffee	*Coffea arabica*	Rubiaceae	Seeds	Caffeic acid, chlorogenic acid	It is effective against Alzheimer's disease.	[27]
Milk thistle	*Silybum marianum*	Asteraceae	Seeds	Silymarin	It acts as a scavenger of free	[28]

Plant	Botanical Name	Family	Part Used	Active Compounds	Properties	References
					radicals and protects the central nervous system against any injury and memory impairment.	
Guggulu	*Commiphora wightii*	Burseraceae	Bark	Ferulic acid, commiphoric acid, eugenol, and commophorinic acid	It acts as a scavenger of superoxide radicals.	[29]
German chamomile	*Matricaria recutita*	Asteraceae	leaves	apigenin	It helps in stimulating the brain and calms the nerves.	[30]
Blueberry	*Vaccinium corymbosum*	Ericaceae	Fruit	Antioxidants, vitamins C, B, β-carotene, lutein, and zeaxanthin	It has anti-inflammatory and antidiabetic, properties, and also helps in preventing Alzheimer's disease.	[31][32]
Rosemary	*Rosmarinus officinalis*	Lamiaceae	Leaves	Carnosic acid, carnosol, rosemanol, rosmarinic acid, and α-pinene	It has antioxidant properties and reduces the risk of AD.	[33]
Snowdrop	*Galanthus nivalis*	Amaryllidaceae	Bulbs	Galanthamine, nivalidine, narwedine, and lycorine	It has antioxidant and antiamyloid activities.	[34]
Turmeric	*Curcuma longa*	Zingiberaceae	Rhizome	Curcumin, bisdemethoxycurcumin, eugenol demethoxycurcumin, zingiberene dihydrocurcumin, azulene, D-camphene, caprylic acid, cineol, and turmerone	It has antioxidant properties so it helps in preventing Alzheimer's disease.	[35][36]
St. John Wort	*Hypericum perforatum*	Hypericaceae	Entire plant	quercetin, Hypericin, rutin quercetin, and isorhamnetin,	It possesses antioxidant and antiamyloid activities.	[37][38]
Black pepper	*Piper nigrum*	Piperaceae	Seeds	piperine	It reduces acetylcholinesterase levels and shows better results in the	[39]

Plant	Botanical Name	Family	Part Used	Active Compounds	Properties	References
					treatment of Alzheimer's disease.	
Garlic	*Allium sativum*	Lilliaceae	Cloves	S-allyl-cysteine, S-allyl-mercaptocysteine Biophenols: caffeic acid, and ferulic acid	It shows antiamyloid and antitangle properties.	[40][41]
Ginkgo	*Ginkgo biloba*	Ginkgoaceae	Leaves	Ginkgolides A, B, C, J and M, bilobalide, quercetin, sesquiterpene kaempferol, and isorhamnetin	It has antioxidant properties. It increases the blood flow in the brain and acts as a scavenger of free radicals and shows neuroprotective properties.	[42][43]
Coriander	*Coriandrum sativum*	Apiaceae	Leaves	Camphor, limonene, alpha-pinene, geraniol, petroselinic acid, and linalool	It helps in improving memory and also helps in managing Alzheimer's disease.	[44][45]
Sesame	*Sesamum indicum*	Pedaliaceae	seeds	Sesaminol, sesamine	It shows neuroprotective properties.	[46]
Apple	*Malus pumila*	Rosaceae	Fruit	Quercetin, catechin, and epicatechin	It improves cognitive functions.	[47]
Ginseng	*Panax ginseng*	Araliaceae	Roots	Ginsenosides, gintonin	It improves the functioning of the central nervous system, and it also shows anti-amyloid activity.	[48][49]
Mulberry	*Morus alba*	Moraceae	Fruit	resveratrol, oxyresveratrol, chlorogenic acid, mulberroside, moracin, and maclurin	It has antioxidant properties and helps in lowering the risk of AD.	[50]
Gotu kola	*Centella asiatica*	Apiaceae	Leaves	Quercetin, myricetin, kaempferol, rutin, and apigenin	It possesses anti-amyloid properties.	[51]
Seneca snakeroot	*Polygala tenuifolia*	Polygalaceae	Roots	Tenuigenin, tenuifolin, and xanthone glycosides	It acts as an acetylcholinesterase	[52][53]

Plant	Botanical Name	Family	Part Used	Active Compounds	Properties	References
					and beta-secretase 1 inhibitor.	
Golden root	*Rhodiola rosea*	Crassulaceae	Roots	Rosavin, salidroside, rosin, cinnamoyl alcohol, and tyrosol	It has very good antioxidant activity and also acts as a cognitive enhancer.	[54][55]
Lemon balm	*Melissa officinalis*	Lamiaceae	Leaves	Citral, protocatechuic acid, caffeic acid, and rosmarinic acid	It acts as a memory enhancer.	[56]
Dwarf periwinkle	*Vinca minor*	Apocynaceae	Upper parts	Vinpocetine, apovincaminic acid, kaempferol glycosides, hydroxybenzoic acids, and chlorogenic acid	It acts as a memory enhancer and also shows antioxidant properties.	[57]
Green tea	*Camellia sinensis*	Theaceae	Leaves	Gallocatechin, Gallic acid, epigallocatechin, epicatechin, epigallocatechin gallate, and caffeine	It possesses antioxidant and antiamyloid activities.	[58][59]
Grapes	*Vitis vinifera*	Vitaceae	Fruit	Resveratrol, quercetin, and catechins	It has antioxidant and antiamyloid properties and is used in preventing neurodegeneration.	[60]
Marijuana	*Cannabis sativa*	Cannabaceae	Bud and leaves	Tetrahydrocannabinol, cannabidiol	It shows antiamyloid activity.	[61]
Olive	*Olea europaea*	Oleaceae	Fruit, oil, leaves	Oleuropein, tyrosol, hydroxytyrosol, caffeic acid, verbascoside, and rutin	It possesses antioxidant, anti-inflammatory, and antiamyloid properties.	[62]
Brazil nut	*Bertholettia excelsa*	Lecythidaceae	Nut	Lecithin	It increases the level of acetylcholine n AD patients.	[63]
firmoss	*Huperzia serrata*	Lycopodiaceae	Aerial parts	Huperzines	It possesses antiamyloid activity.	[64]
Pomegranate	*Punica granatum*	Punicaceae	Fruit	Ellagic acid, gallagic acid punicalagin, and punicic acid	It possesses antioxidant and antiamyloid activities.	[65][66]

Plant	Botanical Name	Family	Part Used	Active Compounds	Properties	References
Marapuama	*Ptychopetalum olacoides*	Olacaceae	Roots	Ptychonal, muirapuamine, and theobromine	It possesses antiamnesic, anticholinesterase, and neuroprotective properties.	[67][68]
Fennel	*Foeniculum vulgare*	Apiaceae	Seed	Estragole, limonene, fenchone, and β-myrcene	It shows an inhibitory effect against acetylcholinesterase and butyrlcholinesterase.	[69]
Papaya	*Carica papaya*	Caricaceae	Fruit	Quercetin, β-sitosterol	It possesses radical scavenging activity.	[70]
Saffron	*Crocus sativus*	Iridaceae	Stigma	Crocin, crocetin, picrocrocin, safranin, and safranal,	It possesses antioxidant and antiamyloid activities.	[71]
Ginger	*Zingiber officinale*	Zingiberaceae	Rhizome	Shagol, gingerol, zingerone	It shows antioxidant properties.	[72]
Sage	*Salvia officinalis*	Lamiaceae	Leaves	Rosmarinic acid, thujone, cineol, and camphor	It shows antioxidant properties. It has cognitive-enhancing properties and helps in preventing age-related problems.	[73]
Camb	*Caryocar brasiliense*	Caryocaracea	Leaf	Gallic acid, quinic acid, quercetin, and quercetin 3-o arabinose	It has neuroprotective effects.	[74]
Coconut	*Cocos nucifera*	Arecaceae	Seed	Caproic acid, Caprylic acid, Capric acid, Lauric acid, and Myristic acid	It helps in preventing Alzheimer's disease.	[75]
Gouteng	*Uncaria rhynchophylla*	Rubiaceae	Stem	Rhynchophylline, isorhynchophylline, and hirsuteine	It shows free radical scavenging activity and also exhibits protection against kainic acid-induced neuronal damage.	[76]
Aloe vera	*Aloe barbadensis*	Aloaceae	Juice	Aloin, β-secretase, aloe-emodin	It improves brain functioning.	[77]

Plant	Botanical Name	Family	Part Used	Active Compounds	Properties	References
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Wuzhuyu	*Tetradium ruticarpum*	Rutaceae	Fruit	Evodiamine, rutaecarpine, evocarpine, and quinoline	It increases the blood flow in the brain and also inhibits the effect of acetylcholinesterase.	[78]
Moringa	*Moring oleifera*	Moringaceae	Leaves	Glycoside niazirin, niaziminim A and B,	It maintains the monoamine level in the brain and helps in treating Alzheimer's disease.	[79]
Walnut	*Juglans regia*	Juglandaceae	Kernel	α-tocopherol, ellagic acid, and juglone	It reduces the risk of Alzheimer's disease by reducing oxidative stress and it also shows amyloidogenic activity.	[80][81]
Cinnamon	*Cinnamomum verum*	Lauraceae	Extract of bark	Cinnamaldehyde, eugenol, and trans cinnamaldehyde	It promotes the disassembly of tau filaments and also shows anti-inflammatory activity.	[82] [44][45]
Tahitian gooseberry	*Phyllanthus acidus*	[93][94] Phyllanthaceae	Fruit	Terpine	It lowers oxidative stress, decreases lipid peroxidation, and helps in increasing the level of antioxidant enzymes in the brain.	[83] [95]
Fig	*Ficus carica*	Moraceae	Fruit	Quercetin, C-Sitosterol	It has antioxidant activity, exhibits memory-enhancing effects and better learning abilities.	[84]
Pumpkin	*Cucurbita maxima*	Cucurbitaceae	seeds	Ferulic acid, caffeic acid, and coumaric acid	It has antioxidant properties and helps in relieving stress.	[85]
Shankhpushpi	*Convolvulus pluricaulis*	Convolvulaceae	Whole plant	Flavonol glycosides, anthocyanins, and triterpenoids	It is consumed as a tonic for enhancing	[86][87]

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impairment was safe and well tolerated [96].

2.2. Gotu Kola

Centella asiatica (family: Apiaceae) is commonly called 'gotu kola'. It is a widespread persistent herbaceous climber in Asia. It is used in traditional medicines for the purpose of regenerating brain cells and enhancing memory, lifespan, and intellect [51]. Animal studies have shown that *Centella asiatica* has an impact on neuronal structure, learning ability, and memory-retaining ability. It has been shown to improve cognitive performance by

Plant	Botanical Name	Family	Part Used	Active Compounds	Properties	References
			[97][98]		memory and it calms the nerves.	[99][100]
Strawberry	*Fragaria ananassa*	Rosaceae	Fruit	Pelargonidin	[101]s antioxidant properties.	[88]
Butterfly pea	*Clitoria ternatea*	Fabaceae	Root and leaf extract	Myricetin, quercetin	It shows antioxidant properties and AChE inhibitor activities.	[89]
Broccoli	*Brassica oleracea* var. *italica*	Brassicaceae	Floret	Kaempferol, sulforaphane	It possesses antioxidant activities and reduces cerebral oedema.	[90]
Spinach	*Spinacia oleracea*	Amaranthaceae	Leaves	Ferulic acid, coumaric acid, quercetin, spinacetin, and myricetin,	It reduces the neuronal death and production of ROS.	[91]
Date palm	*Phoenix dactylifera* L.	Arecaceae	[38] Fruit	Cinnamic acid, caffeic acid, protocatechuic, gallic acid, dactylifiric acid, and epicatechin	It has antioxidant properties and helps in enhancing memory	[92]

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activation of the extracellular signal-regulated kinase (ERK) pathway [42][43]. Numerous studies have connected astrocytosis, microgliosis, and the presence of proinflammatory substances to the deposition of Aβ peptides [102]. *G. biloba* extracts demonstrated therapeutic advantage in AD, compared to donepezil, with few unfavourable side effects. It is most recognized for its capacity to improve circulation (vasorelaxing effect) throughout the body. *G. biloba* can thus reduce blood pressure and prevent platelet aggregation [103]. In an experiment involving 18 randomized clinical trials (RCTs) with 1642 individuals, 842 of them were in the experimental group (donepezil hydrochloride plus *G. biloba* formulations) and 800 were in the control group (donepezil), it was observed that donepezil with *G. biloba* can enhance clinical efficacy rates and verbal memory. However, to validate this, more stringent trials will be required in the future [104].

2.4. Turmeric

Curcuma longa (family: Zingiberaceae) is commonly known as ‘turmeric’. Curcuminoids, such as curcumin, demethoxycurcumin, and bis-demethoxycurcumin, are the phytochemicals present in turmeric. The primary curcuminoid is curcumin, which gives turmeric roots their characteristically yellow colour. According to research, curcumin may be a potential drug for treating AD [105]. The level of oxidative damage in the brain can be reduced by curcumin. It has been shown that curcumin can reverse β-amyloid pathology in a mouse model with AD [106]. The antioxidant and anti-inflammatory properties of curcumin also facilitated in alleviating of some AD symptoms [35][36]. The capacity of the Early Growth Response-1 (Egr1) protein to bind DNA is inhibited by curcumin, which reduces inflammation. Activated microglia and astrocytes produce chemokines which are known to cause monocyte chemotaxis and are also inhibited by curcumin at the CNS. Effective ways to stop proinflammatory cytokine activation include decreasing the production of ROS by stimulating neutrophils and suppressing the tumor necrosis factor α (TNF-α) and interleukin-1 (IL-1) inflammatory cytokine expression [107][108]. Curcumin inhibits the activity of the activator protein (AP-1), a transcription factor involved in the synthesis of amyloid. The capacity of

curcuminoids to prevent the generation and spread of free radicals is proof that they possess potent antioxidant effects. It also prevents the oxidation of free radicals and low-density lipoproteins which causes the destruction of neurons in AD and other neurodegenerative diseases.

2.5. Brahmi

Bacopa monnieri (family: Plantaginaceae) commonly known as 'brahmi' is a persistent creeper that is indigenous to the swamps of eastern and southern India, together with Australia, Europe, Africa, Asia, North and South America, and the Middle East. In traditional medicine, it is frequently used as a cardiotonic, diuretic, and nerve tonic [109][110]. The main phytochemicals of Brahmi are Brahmine, bacosides A and B, apigenin, quercetin, bacosaponins A, and bacosaponins B. Protein kinase activity is increased by *B. monnieri* extracts, which has a nootropic effect. Rats administered Brahmi extract displayed reduced cholinergic degradation and an improvement in cognition. Additionally, it also shields neural cells from the harm done by β-amyloids [110]. *B. monnieri* extract treatment resulted in decreased ROS levels in neural cells, indicating that it reduces intracellular oxidative stress. Cognitive abilities significantly increase with regular use of Brahmi, which also reduced their levels of inflammation and oxidative stress [111]. In addition, a team of researchers found that an extract of standardised *B. monnieri* corrected the cognitive abnormalities brought on by the intracerebroventricular administration of colchicines and ibotenic acid into the nucleus basalis magnocellularis. In the same study, *Bacopa monnieri* also restored acetylcholine depletion, choline acetyltransferase activity reduction, and reduction of muscarinic cholinergic receptor binding in the frontal cortex and hippocampal regions [112]. By suppressing cellular acetylcholinesterase activity, Brahmi extracts prevent beta-amyloid-induced cell death in neurons. In a study (randomized, double-blinded trial) involving 81 persons of the age group 55 and above, a 12-week cycle of Bacopa considerably improved memory acquisition and retention [113].

2.6. Ashwagandha

Withania somnifera (family: Solanaceae) is commonly known as 'ashwagandha' and is regarded as a Rasayana (rejuvenating). It possesses antioxidant properties, characteristic of free radical scavengers. The chemical composition of ashwagandha root includes alkaloids, anolides, many sitoindosides, and flavonoids [114][115]. According to a molecular study, ashwagandha root helps in treating AD by preventing nuclear factor B activation, promoting nuclear factor erythroid 2-related factor 2 (Nrf2) migration to the nucleus, where it enhances the expression of antioxidant enzymes, to reduce the formation of amyloid, decrease apoptotic cell death, restore synaptic function, and boosts the immune system [116]. In certain research, ashwagandha root methanolic preparations were used to treat human neuroblastoma SK-N-SH cells, which led to an increase in dendritic extension, neurite outgrowth, and synapse formation. Researchers have hypothesised that the ashwagandha root extracts are effective in treating neurodegenerative illnesses and also promote neurite growth, and have anti-inflammatory, antiapoptotic, and anxiolytic effects. Moreover, they have the capacity to minimise mitochondrial dysfunctioning, boost antioxidant defence levels, reduce glutathione levels, and can cross the blood–brain barrier and reduce inflammation in the brain [117]. In a double-blind, randomized, placebo-controlled study, 50 participants with moderate cognitive impairment (MCI) were treated with a 300 mg dose of *W. somnifera* root extract twice daily

for an eight-week period. After eight weeks, the *W. somnifera*-treated group displayed considerable improvements in their ability to process information, concentrate, and use executive functions [118].

2.7. Saffron

Crocus sativus (family: Iridaceae) commonly known as 'saffron', possesses antioxidant, anticancer, and aphrodisiac properties and also improves memory in adults. Numerous studies have shown that saffron possesses antioxidative, anti-inflammatory and antiamyloidogenic properties. Additionally, saffron is said to be helpful in reducing acetylcholinesterase and protecting against toxins (AChE). AChE is connected to the neurofibrillary tangles and beta-amyloid plaques that are characteristic of AD [119].

To analyse the effect of saffron on learning abilities, and the prevention of oxidative stress, each rat was administered five and ten grams of saffron extract, twice a week. Oxidative stress markers were assessed seven days later. The group that received saffron treatment was found to have a reduced memory deficit along with enhanced spatial learning and antioxidant activity of enzymes [120]. The main bioactive compound of saffron is crocin. It has the ability to bind to the hydrophobic region of Aβ and thus inhibits its aggregation [121]. A double-blinded/phase II study using the AD assessment scale, cognitive subscale, clinical dementia rating scale, and sums of boxes scores was conducted on a total of 54 patients who were 55 years of age or older with AD. These patients received saffron extractive (30 mg) or donepezil (10 mg) as a positive control once daily for 22 weeks. As a result, donepezil and saffron extractives had similar effects on patients with mild to moderate AD, suggesting that saffron extractives have a therapeutic effect [71].

2.8. Ginger

Zingiber officinale (family: Zingiberaceae) commonly called 'ginger' is a spice having both culinary and therapeutic uses. It is frequently used as a nutritional supplement, in ginger tea preparation, or as an extract. The primary bioactive components in ginger include gingerols, shagols, volatile oils such as bisabolene and zingiberene, and monoterpenes. In vitro research has been done on the AChE inhibitory activity of red and white ginger [122]. Inhibition of AChE causes acetylcholine to accumulate in synapses, which is followed by an increase in the cholinergic pathway activity and results in better cognitive performance in AD patients.

Ginger's ability to decrease lipid peroxidation is vital for the prevention of AD. Pro-oxidants such as quinolinic acid (QUIN) and sodium nitroprusside (SNP) are utilised to cause lipid peroxidation in the rat-brain homogenate. Due to the overstimulation of NMDA receptors and the significant rise in malondialdehyde level brought on by the incorporation of SNP and QUIN, free radicals are produced [72]. Ginger extract was demonstrated to boost brain SOD and CAT expression, decrease NF-κB, interleukin-1 beta (IL-1β), and malondialdehyde (MDA) levels and improve behavioural impairment in a rat model of AD caused by oral $AlCl_3$ and injection of intracerebroventricular β-amyloid protein [123]. In a similar study, the fermented ginger extract had more bioavailability and has been shown to greatly reduce synaptic dysfunction and neuron cell loss, compared to the fresh extract, in a mouse model of AD produced by injection of β-amyloid plaques [124].

2.9. Rosemary

Rosmarinus officinalis (family: Lamiaceae) is commonly called ‘rosemary’. Other than its native Mediterranean region, several other countries are known to use the plant in traditional medicine.

It possesses antioxidant and anti-inflammatory properties. To learn how drinking rosemary tea affects the working of the brain, an investigation on adult male mice was done. The testing revealed that rosemary tea consumption for four weeks had a favourable effect (anxiolytic- and antidepressant) without changing the memory or learning [29]. Other researchers have shown that it possesses antidepressant properties and is able to reverse ACHE changes despite spatial learning impairment [125]. Carnosic acid has also been found to have neuroprotective effects on cyanide-induced brain damage in cultured rodent and human-induced pluripotent stem cell-derived neurons in vitro and in vivo in several brain locations in a non-Swiss albino mouse model [126]. In vitro, the intercellular adhesion molecule (ICAM-1) expression is suppressed and tumour necrosis factor (TNF)-induced monocyte adherence to endothelial cells is inhibited by carnosol and rosemary essential oils [127]. Carnosol decreases the activity of the nuclear factor kappa-B inhibitor and increases the production of heme oxygenase-1 (HO-1), both of which block the signalling pathways triggered by TNF-α [128]. According to a study conducted on 68 students in Kerman, Iran, using 500 mg of rosemary twice daily for a month improved students’ prospective and retrospective memory [129].

2.10. Date Palm

Phoenix dactylifera (family: Arecaceae) is commonly called ‘date palm’. They have been used since Mesopotamian civilization, and their historical, theological, and medicinal significance is well known [130][131]. Three to four date fruits per day were recommended for improving memory in Palestine [131]. Turkish people drink “Hurma coffee,” an herbal brew made from date fruit seeds, to improve their memory. It reduces glutathione, glutathione reductase, and glutathione peroxidase levels [132]. In addition, mice with AD were fed diets supplemented with 2 and 4% acetone-extracted date fruit, for 14 months, and the results were compared to mice receiving a control diet. When mice were fed dates at 2 and 4% levels, oxidative stress markers such as protein carbonyl levels, lipid peroxidation, and the restoration of anti-oxidative stress enzymes were all considerably reduced [133].

2.11. Pumpkin Seeds

Cucurbita maxima (family: Cucurbitaceae) is commonly known as ‘pumpkin’. Pumpkin seeds are included in the category of nuts. Despite their significant nutritional content and therapeutic qualities, pumpkin seeds are typically seen as agricultural waste and are thrown away. In addition to being added to food preparations, they can be eaten in their fresh or roasted form. Pumpkin seeds are rich in choline (63 mg/100 g) and L-tryptophan (576 mg/100 g) [11]. L-tryptophan is frequently used to treat a variety of medical disorders, including anxiety, sleeplessness, and depression [134][135]. The body can convert tryptophan to serotonin, which in turn may control a number of cognitive functions. It is known that choline serves as a precursor for the synthesis of the neurotransmitter acetylcholine in cholinergic synapses, which deliver stimulatory signals to nerve cells. Moreover, choline promotes brain growth [136]. In adult male Wistar rats, oral treatment of pumpkin-seed oil (100 mg/kg and 200 mg/kg for 5 days) is reported

to have antiamnesic benefits against scopolamine-induced amnesia. It suppresses acetylcholine esterase, reduces TNF expression in the hippocampus, and raises glutathione levels in the brain [136].

2.12. Garlic

Allium sativum (family Liliaceae) is commonly known as 'garlic'. It is widely used in traditional medicines for the treatment of numerous diseases, including AD. The most popular garlic preparation used is called AGE, and it is often made by keeping slices of garlic in a solution of water and ethanol for more than 10 months at ambient temperature. Aggregation of unusually folded Aβ and tau proteins in amyloid plaques and neuronal tangles are the main pathologies of AD. The two primary types of Aβ are Aβ40 and Aβ42. AGE at dosages of 250 and 500 mg/kg BW can improve short-term memory deficits in humans [40][41]

It has been discovered that raw garlic has strong antineuroinflammatory capabilities, and this is due to organosulfur compounds (OSCs) that are produced from alliin (such as allicin, diallyl trisulfide, and diallyl disulfide). In lipopolysaccharides (LPS)-activated microglial cells, these substances, particularly diallyl trisulfide and diallyl disulfide, reduce the generation of TNF-α, lipopolysaccharide (LPS) induced nitric oxide, monocyte chemoattractant protein-1, and interleukin-1 (IL-1) [137]. Similar to this, glial cell activation caused by LPS and inflammatory mediators that are implicated in amyloidogenesis is reduced by the sulphur-containing substance thiacremonone [138].

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