

Complementary and Alternative Medicines Use Against Neurodegenerative Diseases

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Abstract The incidence of neurodegenerative diseases is rising due to rapidly aging population around the world and it is estimated that by 2040 they would surpass cancer as the principal cause of death in industrialized countries. Neurodegenerative diseases are relentlessly progressive disorders of the central nervous system characterized by cognitive, motor and/or behavioral dysfunctions. These diseases include Alzheimer's (AD) and Parkinson disease (PD) as most common ones and less commonly amyotrophic lateral sclerosis, Huntington's disease and vascular dementia. Despite tremendous advances in the understanding of these diseases, pharmacological treatment by conventional medicine has not obtained satisfactory results. For instance, pharmacological therapies for AD such as acetylcholinesterase inhibitors and for PD such as Levodopa are merely symptomatic. This coupled with the fact that they exhibit various side effects have led to the use of complementary and alternative medicine for the management of AD and PD. This review attempts to explore some of the most commonly used complementary and alternative medicine against AD and PD

Keywords Complementary and Alternative Medicines, Neurodegenerative Diseases, Alzheimer, Parkinson Disease

1. Introduction

Neurodegenerative diseases are relentlessly progressive disorders of the central nervous system (CNS) characterized by cognitive, motor, and/or behavioral dysfunction [1]. Aging is a major risk factor of neurodegenerative diseases [2]. The age related neurodegenerative diseases that are now epidemic include Alzheimer's disease (AD) and Parkinson's disease (PD), the most common neurodegenerative dementia and movement disorder, respectively, and the less common conditions like amyotrophic lateral sclerosis (ALS), Huntington's disease (HD) and vascular dementia (VaD) [3].

Abnormal protein aggregation represents a unifying biochemical and histomorphological hallmark of neurodegenerative disease. In most cases, these protein aggregates form microscopically-visible cellular deposits called "inclusion bodies" [1]. These include β -amyloid peptides and tau/phosphorylated tau proteins in AD, α -synuclein in PD, superoxide dismutase in amyotrophic lateral sclerosis, and mutant huntingtin in Huntington's diseases [2]. It is thought that the degenerative process is underway for many years before symptoms become evident [4].

The incidence and prevalence of these disorders are on the rise due to worldwide demographic trends that are leading to rapidly aging populations across the globe [3]. The World Health Organization (WHO) estimates that, by 2040, neurodegenerative diseases will surpass cancer as the principal cause of death in industrialized countries [5].

Despite various advances in the understanding of the diseases, pharmacological treatment by conventional medicine has not obtained satisfactory results. Therefore, complementary and alternative medicine (CAM) can be a potential candidate for the preventative treatment of the disorders [5]. CAM refers to "a group of diverse medical and health care systems, practices, and products that are not presently considered to be part of conventional medicine" [6]. The CAM therapies are classified into five categories:

- whole medical systems (traditional Chinese medicine, Ayurvedic medicine, homeopathy, and naturopathic medicine)
- mind-body medicine (meditation, prayer, yoga, tai chi, biofeedback, relaxation, and art, dance and music therapies)
- biologically-based therapies (herbal preparations, botanicals, and dietary supplements)
- manipulative and body-based methods (chiropractic, therapeutic massage, and osteopathic manipulation)
- energy therapies (Reiki, therapeutic touch, and bioelectromagnetic-based therapies) [7,8].

In this review, we discuss the various CAM used in the management of neurodegenerative diseases, namely AD and PD.

2. Alzheimer's Disease

AD is a neurodegenerative disease characterized by progressive cognitive decline leading to complete need for care within several years after clinical diagnosis. It is a major cause of dementia in people aged over 60 years [9]. An estimated 5.2 million people in United States of all ages have AD in 2013 and by 2050, this number is projected to nearly triple, from 5 million to a 13.8 million [10]. The disease is symptomatically characterized by progressive memory deficits, cognitive impairments, and personality changes [11].

The pathological features of AD, although not yet fully understood today, comprise of senile plaques (SP) and neurofibrillary tangles (NFT). These features are responsible for the characteristic massive neuronal loss observed in AD patients, mainly in the hippocampus and associated regions of the neocortex [12].

It has long been argued that AD is intrinsic to aging. Nevertheless, this does not take into consideration that although AD symptoms only become recognizable in old age and at an advanced phase of the disease-related process, the clinically mute, but pathological, process exists much longer, suggesting that AD might have one of the longest prodromal phases of all known neurodegenerative diseases [13].

2.1. Pathogenesis of AD

2.1.1. Amyloid β Peptide 42

The histopathological hallmark of AD is the deposition of senile plaques in the neuropil of the cerebral cortex and hippocampus, whose primary component is the $A\beta$ peptide. This 40–42 amino acid peptide is widely regarded as a major contributor to the neurodegeneration that occurs in AD brains [14]. It has been demonstrated that elevated plasma $A\beta_{42}$ levels correlate with increased risk of AD. $A\beta$ is the product of the proteolytic processing of its precursor, β -APP (or simply APP), resulting from sequential cleavage by proteases named β - and γ -secretases [15]. The amyloid cascade hypothesis initially attributed pathogenesis to a conformational change, i.e., increased β -sheet secondary structure, and therefore decreased solubility, fibrillization, and nucleation of a toxic protein substance, amyloid, within the brain [16]. Mutations in both the APP and presenilin (PS-1 and PS-2) genes have been associated with familial AD (FAD) which is inherited in an autosomal dominant fashion [14,16]. These genes contain manipulable, methylated CpG sites. It has been demonstrated that in AD patients the promoter region of the APP gene is hypomethylated, which apparently enhances $A\beta$ production [12].

2.1.2. Neurofibrillary Tangles

The second major pathological feature of AD is NFT [12]. The main component of NFT is an abnormally phosphorylated microtubule associated tau protein [13]. In AD, hyperphosphorylated tau aggregates, reducing its ability

to bind microtubules and leading to cytoskeletal degeneration and neuronal death [12]. Tau lesions are present from the beginning until the end phase of the disorder and are not known to be subject to remission. Abnormally phosphorylated tau tends to form non-biodegradable aggregates which accumulate intra-neuronally initially as non-fibrillar and non-argyrophilic inclusions and referred to as "pretangles" [13]. Pretangle material can (but does not always) evolve into rigid fibrillar and argyrophilic neuropil threads (NTs) in dendritic processes and neurofibrillary tangles (NFTs) in cell bodies. From the tau phosphorylation hypothesis, it has been deduced that the locus coeruleus is most probably the site where AD begins [13].

The intra-neuronal disease progresses in a topographically systematic manner, divided into six NFT stages. It has been found out that neurons which are more susceptible to tau lesions are those which develop postnatally and thus which have disproportionately lengthy and weakly myelinated axons [13]. It has further been postulated that the accumulation of $A\beta$ in turn facilitates tau phosphorylation by kinases like GSK3 [17]. Tau pathology starts in the entorhinal cortex, from where it spreads to neighboring regions, like the hippocampus [17] through nerve cell to nerve cell propagation of phosphorylated tau [16].

2.1.3. AD and Advanced Glycated End Products

Advanced Glycated End Products (AGEs) are markers of carbonyl stress, which accumulate due to an increased level of sugars and reactive dicarbonyl compounds such as glucose, fructose, deoxyglucose, glyoxal, methylglyoxal and triosephosphates [18]. AGEs are formed as a consequence of oxidative stress but the subsequent formation of AGEs could in turn induce oxidative stress, suggesting a positive feedback loop which increases the level of oxidative damage in the brain [19]. AGE formation is irreversible and causes protease-resistant cross-linking of peptides and proteins, leading to protein deposition and amyloidosis. AGEs can damage cells by a multitude of processes including direct neurotoxicity involving oxidative stress and apoptosis. Methylglyoxal (MG) has been suggested to be one major source of intracellular reactive carbonyl compounds, and has been implicated in the increased AGE levels in age-related diseases including AD [18].

The aggregation and deposition of proteins derived from AGE modification and the resulting cross-linking have been observed in both plaques and tangles [19]. AGE formation may occur in the early stages of plaque formation in AD, but that AGE-epitopes disappear when the plaque ages or undergoes processing by microglia in the amyloid core [14]. Moreover, recent data showed that APP expression was up-regulated by AGEs in vitro and in vivo, leading to an increased β -amyloid level [19].

It has also been shown that AGEs contribute to the formation and toxicity of NFTs. Interestingly, a recent study reported that AGEs could induce tau protein hyperphosphorylation and impair synapse and memory in rats likely through RAGE mediated GSK-3 activation [19].

The presence of various MG-derived AGEs has been noted in intracellular protein deposits NFTs [18]. The protein constituents of NFT are resistant to proteolytic removal, possibly as a result of extensive disulfide, dityrosine and AGE cross-linking, thus, reinforcing the hypothesis that AD is a disease characterized by an imbalance of proteolytic regulation [14].

2.1.4. The Epigenetics of AD

AD can have an early (familial) or late-onset form, and the risk for both forms is increased by mutations in APP, presenilin (PS) and apolipoprotein E4 (ApoE4) genes [20]. More specifically early onset AD (EOAD) (<60 years of age) is associated with APP or the presenilins, whereas the risk to develop late onset AD (LOAD) is linked to an ApoE polymorphism [21]. A striking feature of AD is that most cases are sporadic, with dominantly inherited forms accounting for less than 1% of the total [22] and the inheritance of known mutations that predispose to FAD accounts for only 5–10% of all clinically presented cases [23].

Epigenetics deals with acquired and heritable modifications on DNA that regulate the expression and functions of genes without affecting the DNA nucleotide sequence. These include DNA methylation and hydroxymethylation, histone modifications and non-coding RNA regulation [24]. Epigenetic mechanisms are thus thought to mediate the interaction between genetic and environmental factors. AD patients have dysregulated DNA methylation, and altered expression of AD susceptibility genes [20].

Numerous studies suggest that a genome-wide decrease in DNA methylation is present in the aging and AD patient [12]. Hypomethylation of the GC-rich APP promoter was reported to correlate with APP over-expression in AD. Moreover, DNA methylation controls BACE and PS1 expression and consequently, all these factors contribute to an increased A β level [24]. Histone post-translational modifications are also dysregulated in AD and histone acetylation is overall increased in the AD brain [20]. Various microRNAs are differentially expressed in AD and alter the expression of AD pathological intermediates. An example is microRNA-101 which negatively regulates APP levels and is reduced within the brain cortex of AD patients [24].

A major genetic risk for LOAD is the ApoE ϵ 4 allele, with data showing that 40–80% of patients with sporadic AD possess at least one ϵ 4 allele [23]. ApoE ϵ 4 carriers have a greater probability of developing AD at an earlier age. Even though the onset of AD is at an earlier age, the rate of disease progression seems to be similar to non-ApoE ϵ 4 carriers. Moreover, it has been found that there is a significant ApoE isoform dependent accumulation of A β such that the amount of brain A β deposition is greatest and significantly larger in size in ApoE ϵ 4 carriers [25].

2.1.5. Oxidative Stress in AD

Substantial research demonstrates oxidative stress in AD

as yet another potentially important pathogenic mechanism [16]. There is a growing body of evidence indicating changes in the redox status of AD brains. This is supported by findings of increased levels of oxidative damage markers in every major cellular macromolecule (proteins, lipids, and DNA). Also, alteration in the expression of antioxidant systems lends support to a role for free radical damage in AD pathology [21].

Oxidative damage to DNA can be highly detrimental to its function and viability. 8-oxo-7,8-dihydro-2'-deoxyguanosine (8-oxodG) is the most prevalent form of oxidative base modifications produced in DNA. Some evidence suggests that in addition to its mutagenic properties, the presence of 8-oxodG in DNA can alter binding of transcription factors and have an impact on epigenetic signaling [21]. One of the more recent findings is that RNA oxidation may induce sub-lethal changes within the cell that results in aberrant translation and exacerbation of chronic disease [16].

2.1.6. Mitochondrial Pathology in AD

Mitochondrial alterations in particular, such as fission-fusion abnormalities, defects in electron transport chain proteins, and cytoskeletal abnormalities that may impair mitochondrial movement and therefore biology, have all been shown to be altered in AD [16]. Moreover, calcium metabolism, intrinsic apoptosis pathways and activation of caspases and generation of free radicals are also to be considered in AD pathology mediated by the mitochondria [16].

2.2. Pharmacological Therapies against AD

AD represents one of the most formidable challenges to the drug discovery community [26]. Therapeutic approaches to AD are symptomatic and of modest efficacy. Two classes of drugs currently approved for use by the FDA include the acetylcholinesterase inhibitors, namely donepezil, galantamine and rivastigmine and the N-methyl-D-aspartate (NMDA) receptor antagonist memantine [9]. Acetylcholinesterase inhibitors are indicated for patients with mild to moderate symptoms while memantine is recommended for moderate to severe cases of AD [27].

A new target for therapeutic approaches in AD is the development of disease-modifying drugs. These will presumably be drugs that will modify by stabilizing or slowing, the molecular pathological steps leading to neurodegeneration and finally dementia. However, the concept of disease modification in AD is still controversial. Currently, disease modifying drugs are being pursued against amyloid deposition, tau deposition, inflammation and oxidative stress [9]. Nevertheless none of these approaches have so far led to new medicines to combat AD [26].

Another approach being investigated is targeting the mitochondria which are involved in the pathology of AD. As such MitoQ, an orally active antioxidant currently in

development by Antipodean Pharmaceuticals Inc, is now undergoing Phase II clinical trials for the potential treatment of neurodegenerative diseases. MitoQ which comprises of a ubiquinone moiety is believed to be a promising antioxidant candidate for treating AD patients [26].

The therapeutic limitations of acetylcholinesterase inhibitors along with pharmacological side effects of these interventions [27] and the steadily increasing prevalence of the disease [28] have led to the use of CAM for the management of AD [5].

2.3. Traditional Chinese Medicine

Traditional Chinese medicine (TCM) is practiced in the Chinese health care system for more than 2,000 years [29]. According to TCM, aging is regarded as a process of progressive decline of “vital energy” in our body; and therefore leads to deterioration in functions and diseases [30]. Thus, Chinese herbs provide a good source of drugs for screening that may be beneficial for AD patients. In recent years, scientists have isolated many novel compounds from herbs, some of which improve dementia with fewer side effects than conventional drugs and are regarded as promising anti-AD drugs [29].

2.3.1. *Ginkgo biloba*

Ginkgo biloba L. has customarily been used in China as a medicine to promote vitality in humans. Some of its main active ingredients which are attributed to its memory enhancing effects are ginkgolides, bilobalide, ginkgolic acids, and ginkgo flavone glycoside [29]. EGb761 is a standardized extract of the leaves of the *G. biloba* tree and is characterized by its main fractions, the flavonols (mainly isorhamnetin, kaempferol and quercetin: 22–27%) and the terpene lactone (5–7%). These two fractions are thought to be, at least partly, responsible for potential neuroprotective properties of EGb761 [31].

A clinical trial concluded that the *G. biloba* extract EGb 761, specifically at a 240 mg daily dose, was both safe and effective in the treatment of patients with dementia associated with neuropsychiatric features [32]. Moreover, another clinical trial showed that the net effect of EGb761

treatment on cognitive and functional abilities increases with increasing neuropsychiatric burden at treatment outset [33]. A clinical trial has proved its safety and efficacy in the treatment of both major types of dementia, AD and Vascular Dementia [34].

However, the efficacy of *G. biloba* in AD has been largely debated. A 6 months regulatory trial carried out to obtain FDA marketing approval for EGb761 did not show efficacy for mild-to moderate AD. Furthermore, the Ginkgo Evaluation of memory trial demonstrated that *G. biloba* does not prevent dementia in elderly individuals with or without memory complaints or cognitive impairment and is not effective for prevention of AD [35].

Few clinical trials have tried to examine the effectiveness of *G. biloba* in preventive AD. Among these preventive trials is GuidAge - a multi-centre, randomized, double-blind, placebo-controlled, parallel-group, 5 year study- conducted in 13 subgroups in France. The research has aimed to assess the efficacy of long term daily administration of 240 mg of a standardised *G. biloba* extract in lowering the risk of AD. The study was unsuccessful in showing the protective effects of *G. biloba* for the incidence of AD [36].

Finally, in a meta-analysis review, the authors concluded that despite promising results, broad recommendations for the use of *G. biloba* in neuropsychiatric conditions, such as AD are still premature [37].

2.4. Ayurvedic Medicine

The Indian system of holistic medicine known as Ayurveda uses mainly plant-based drugs or formulations to treat various ailments [38]. Rasayana tantra, one of eight major disciplines in Ayurveda is defined as a treatment to attain longevity, intelligence, freedom from age related disorders, youthful appearance, optimum strength of physique and sense organs, maintain language ability and improve memory [39]. A number of herbs and herbal preparation have been documented relevant to AD in the Ayurveda. Table 1 illustrates various plants used in traditional systems around the world for the management of dementia and AD.

Table 1. Plants used in the management of AD

Plant/family	Mechanism of action	Traditional uses	References
<i>Angelica archangelica</i> L. Apiaceae	Crude alcohol extracts have inhibited AChE activity <i>in vitro</i> .	Commonly used in Chinese medicine for cerebral diseases.	[40]
<i>Artemisia absinthium</i> L. Compositae	The crude alcohol extract shows good antioxidant activity and favorable effects in the CNS. It may be appropriate in the treatment of AD.	Widely used as an anthelmintic. Traditionally used for lost or declining cognitive function	[40,41]
<i>Bacopa monniera</i> L. Plantaginaceae	Extract of this plant could improve ACh and cerebral blood flow. The GABAergic system could also be involved in the mediation of CNS effects. The extracts have nootropic, anti-amnesic, anti-stress, anticonvulsive, antidepressant, and anxiolytic effects. A combination of <i>B. monniera</i> with rivastigmine was found to be more effective than either treatment alone in preventing AlCl ₃ -induced learning and memory deficits.	Commonly used in a traditional system of Ayurvedic medicine as nerve tonic, diuretic, cardiogenic and therapeutic agents against epilepsy, insomnia, asthma and rheumatism.	[40,42,43]
<i>Berberis aristata</i> Berberidaceae	Berberine exerts anti-depressant-like effect in various behavioral paradigms of despair, possibly by modulating brain biogenic amines (norepinephrine, serotonin and dopamine).	Its herbal formulations are used to treat malaria, bleeding, fever, skin and eye infections, jaundice, diarrhea and hepatitis for a long time in Ayurvedic medicine. In Garhwal Himalaya, it is used as a psychomedicines for treating exorcism in children.	[44]
<i>Centella asiatica</i> L. Apiaceae	The triterpene Asiatic acid show strong protective effect reducing H ₂ O ₂ -induced cell death and lowering intracellular free radical concentration. Asiatic acid and its derivatives have been also been shown to protect cortical neurons from glutamate-induced excitotoxicity <i>in vitro</i> .	The whole plant is used as a nervine tonic in various brain diseases and given to children as syrup to increase the memory. It is thought to be effective for impaired intelligence and as a rejuvenator. In parts of India it is given with milk to improve memory against dementia and aging.	[39]
<i>Chamaecrista mimosoides</i> L. Greene Caesalpinaceae	The DCM:MeOH extracts of <i>C. mimosoides</i> roots showed good antioxidant and cholinesterase inhibitory activity.	Cold water root infusions of <i>C. mimosoides</i> are reported to be taken to remember forgotten dreams by the Zulu.	[45]
<i>Coptis chinensis</i> Franch. Ranunculaceae	Berberine, isolated from the rhizome, modulates the APP proteolytic process to reduce the production of A β peptides. The alkaloids also are AChEI, and the plant has improved a scopolamine-induced learning and memory deficit in rats.	Used for several conditions including age related cognitive and memory decline.	[39,40,46]
<i>Crinum moorei</i> Hook.f. Amaryllidaceae	Like many members of the Amaryllidaceae family, 1- <i>O</i> -acetyllycorine isolated from the bulb show AChE inhibitory activity comparable to galantamine.	Used in Southwest Nigeria by traditional healers for memory loss and other mental ailments associated with aging.	[39,47]
<i>Curcuma longa</i> L. Zingiberaceae	Curcumin may improve cognitive function in the elderly which is demonstrated by better cognitive abilities in elderly populations who consume turmeric regularly. Curcumin may play a dual role in protecting neuron against the Cu (II)-induced oxidative damage involved in AD. Other pharmacological activities include anti-inflammatory and antioxidant properties.	In Ayurvedic medicine, curcumin is a well-documented treatment for various respiratory conditions (e.g., asthma, bronchial hyperactivity, and allergy) as well as for liver disorders, anorexia, rheumatism, diabetic wounds, runny nose, cough, and sinusitis.	[38,48]
<i>Cynodon dactylon</i> L. Pers. Poaceae	It has reported antioxidant properties.	The juice is used in Ayurvedic medicine for hysteria, epilepsy and insanity.	[49]
<i>Cyperus rotundus</i> L. Cyperaceae	It has reported antioxidant properties.	It forms an ingredient of Amrita Bindu, a salt-spice-herbal mixture based on Indian system of medicine that can control inflammation and degenerative disorders, slowing the aging process.	[49]
<i>Damnacanthus officinarum</i> Huang Rubiaceae	Extracts of DOH could delay aging and prolong lifespan of <i>Caenorhabditis elegans</i> study models. Anthraquinones and glycosides are thought to be its major active components.	DOH has been used in Southeast China as Yang-tonic agent. DOH root has also been used to treat nervous system syndromes, such as depression, dementia and fatigue. It is an important component in Dihuang Yinzi decoction formula, which has been widely used in clinic and proved to be effective in treatment of brain stroke and dementia.	[50]

<i>Emblica officinalis</i> Gaertn. Phyllanthaceae	Indian Ayurvedic herbal preparation Anwala churna lowered serum cholesterol in mice, elevated ACh level in brain and ultimately improved memory of both young and aged mice, through the antioxidant properties of <i>E. officinalis</i> .	In Unani medicine, it is described as a tonic for heart and brain. It is an important in many herbal preparations such as Triphala and Chyawanprash which possess anti-aging properties while improving mental faculties and rejuvenative and co-ordination and memory enhancing properties respectively.	[51]
<i>Epimedium koreanum</i> L. Berberidaceae	Methanolic extracts show significant cholinesterase inhibition.	Used in traditional Korean medicine for improvement of memory and cognition in old age.	[52]
<i>Evodia rutaecarpa</i> Rutaceae	The alkaloids, dehydroevodiamine and rutaecarpine have inhibited AChE in vitro and have reversed scopolamine-induced memory impairment in rats.	In Chinese medicine, the plant is used for cardiostimulant and analgesic purposes.	[40]
<i>Evolvulus alsinoides</i> L. Convolvulaceae	Both ethanolic extract and water infusion of <i>E. alsinoides</i> have been found to have antioxidant effects, shown by the inhibition of lipid peroxidation.	In India it is used in insanity, epilepsy and nervous debility. In Ayurveda it is used for the treatment of degenerative diseases.	[49]
<i>Ferula asafoetida</i> Boiss. Apiaceae	Gum extract shows potent activity against COX-1 suggesting an effective new and promising agent for treatment of AD.	Egyptian herbal medicine used as a strong aphrodisiac, strong nerve tonic, relieving on-going mental and physical fatigue	[53]
<i>Huperzia serrata</i> Thunb. Lycopodiaceae	Huperzine A shows reversible and selective inhibition of AChE. In a multicentered, double-blind trial, huperzine A significantly improved memory and behavior in patients with AD. It is reported have less side effects and longer duration of action than the synthetic AChE inhibitors donepezil and tacrine.	Huperzia serrata has been used in TCM to promote circulation, reduce fever, and provide anti-inflammatory and analgesic effects. The prescription drug Qian Ceng Ta (prepared from <i>Huperzia serrata</i>) has been used to alleviate problems of memory loss.	[40,29]
<i>Lycium barbarum</i> L. Solanaceae	<i>L. barbarum</i> polysaccharides (LBP) have direct cellular protection against A β neurotoxicity. LBP can attenuate glutamate excitotoxicity in vitro, and its protective effect is comparable to Memantine.	The fruit belongs to “Yin tonifying herb” and is believed to be effective in replenishing any deficient “Yin” associated with aging; hence balancing homeostasis in the body.	[30]
<i>Magnolia officinalis</i> Rehd. et Wils. Magnoliaceae	Honokiol and magnolol increased choline acetyltransferase (ChAT) activity, inhibited AChE activity in vitro, and increased hippocampal Ach release in vivo. Antioxidant and anti-inflammatory activities also have been reported.	Commonly used in Chinese medicine, the bark of the stem and the roots are used to treat anxiety and nervous disturbances.	[40]
<i>Melissa officinalis</i> L. Labiatae	The leaf extracts have antioxidant effects and binding to muscarinic and nicotinic receptors in vitro, which suggests that favorable effects on cholinergic function may occur in patients with AD. The plant's potential effectiveness to alleviate nervousness and anxiety has been confirmed in a double-blind study. This suggests that it may be appropriate to provide symptomatic relief for behavioral problems such as agitation in AD.	The leaves have been used medicinally for more than 2000 years. In Europe, it was used as a calming and strengthening remedy and to treat migraines, melancholia, neuroses, and hysteria. Also, the plant has been acclaimed for promoting long life and for restoring memory. Also used to sharpen the senses and to strengthen the brain.	[39,40]
<i>Mentha aquatica</i> L. Labiatae	Naringenin has an affinity to the GABAA benzodiazepine receptor and reportedly has MAOI activity. It is a potential antioxidant, capable of scavenging free radicals, and modulating the activities of antioxidant enzymes.	The dried leaves of <i>Mentha aquatica</i> together with those of <i>Tagetes minuta</i> L. are burned and the smoke inhaled by the Venda people of South Africa to treat mental illnesses.	[40,54,55]
<i>Physostigma venenosum</i> Leguminosae	Physostigmine as a short-acting reversible AChEI is reported to have shown significant cognitive benefits in in patients with AD. It has been reported to protect mice against cognitive impairment caused by oxygen deficit; it improved learning in rats, and antagonized scopolamine-induced impairment of cognitive function in rats. In fact, the chemical structure of physostigmine has provided a template for the development of rivastigmine.	The seeds of this plant, indigenous to Calabar on the coast of Nigeria in West Africa, were used by local people for “trial by ordeal” to determine the guilt or innocence of an accused criminal.	[40,47]
<i>Polygala tenuifolia</i> Willd.	The root extract alone could up-regulate ChAT activity. Increased nerve growth factor secretion	The root is used in TMC as a cardiostimulant and cerebrotonic; as a sedative and tranquilizer; and for	[40]

Polygalaceae	in vitro may be due to the cinnamic acid derivate, sinapinic acid.	amnesia, forgetfulness, neuritis, nightmares, and insomnia.	
<i>Polygonum multiflorum</i> Thunb. Polygonaceae	Tetra hydroxyl stilbene glucoside enhances learning memory abilities in APP mice. Ethanol extracts of the roots of the herb show good inhibitory effects on A β generation with possible novel anti-AD activities.	The dried roots of <i>Polygonum multiflorum</i> Thunb have been used as a tonic and an anti-aging agent in many remedies in traditional Chinese medicine.	[46,56]
<i>Pterocarpus erinaceus</i> Poir. Fabaceae	Aqueous extract of the bark decreases β -amyloid peptide production.	In Benin, the stem bark decoction is used against anemia, dysentery and growth or learning retardation.	[57]
<i>Rosmarinus officinalis</i> L. Labiatae	The essential oil and its monoterpene constituents have shown weak inhibitory AChE activity. Its antioxidant activity, mainly due to the presence of flavonoids, may therefore have relevance in disorders involving oxidative stress such as in AD.	As a circulatory stimulant for improving concentration and memory. Often used by herbalists and aromatherapists for memory problems.	[39,40]
<i>Salvia lavandulaefolia</i> Vahl. Labiatae	The cholinesterase inhibition shown by the essential oil is likely due to the cyclic monoterpenes 1,8-cineole and α -pinene, perhaps by acting synergistically with other constituents.	Research into historical literature has revealed that some activities of Spanish sage particularly its reputation as being good for the memory, may be relevant in the treatment of AD.	[40]
<i>Salvia miltiorrhiza</i> Bunge. (Danshen) Labiatae	They can inhibit A β peptide fibril aggregation and A β production respectively.	The dried root of Chinese sage is used in medicine to stabilize the heart and calm nerves. Official indications for the root include treatment of blood circulation disorders, insomnia, neurasthenia, and alleviation of inflammation.	[40,46]
<i>Salvia officinalis</i> L. Labiatae	An ethanol extract from the steam-distilled oil has shown anti-ChE activity, and it has been suggested that sage might be of possible use in treating Alzheimer's disease.	Remedies help those who shiver and suffer the effects stroke and strengthen weak minds and memories and used against dementia	[39,40]
<i>Stephania suberosa</i> Menispermaceae	Methanolic extracts of the roots of the plant show significant AChE inhibition.	Used in Thai traditional rejuvenating and neurotonic remedies	[52]
<i>Thespesia populnea</i> (L.) Sol. Malvaceae	May prove to be a useful medicine because of its multifarious beneficial effects such as improving memory, lowering cholesterol, and AChE and its anti-inflammatory and antioxidant activities.	In the indigenous system of medicine, the paste of the fruits, leaves and roots of <i>T. populnea</i> are applied externally for various skin diseases. The leaves are applied locally for their anti-inflammatory effects in swollen joints.	[40,58]
<i>Uncaria rhynchophylla</i> (Miq.) Jacks. Rubiaceae	It was reported that the extracts from <i>U. rhynchophylla</i> have significant inhibitory and destabilizing effects on A β fibril than other Chinese medical herbs	It has been used to alleviate neuropsychiatric symptoms, such as headache, dizziness, vertigo, and tinnitus.	[29]
<i>Uncaria tomentosa</i> Willd. Rubiaceae	The alkaloid components have shown to improve memory function in mice with experimental amnesia. More specific to AD, a proprietary extract of <i>Uncaria tomentosa</i> potently inhibits β -amyloid fibril formation and even solubilizes preformed amyloid fibrils.	It has traditionally been used by Ashaninka Indians to treat disorders including arthritis, heart disease, cancer, and other inflammatory diseases.	[40,59]
<i>Withania somnifera</i> (L.) Dunal Solanaceae	Sitoindosides VII-X, and withaferin-A, isolated from aqueous methanol extract from the roots augmented learning acquisition and memory in both young and old rats most probably through modulation of cholinergic neurotransmission. Withanolide A modulates APP metabolism by down regulating BACE-1. The glycowithanolides have shown anxiolytic and antidepressant activities in rats along with calcium antagonistic ability which could make the withanolides possible drug candidates for further study to treat AD.	Ashwagandha has been extensively used for centuries in Ayurvedic medical practice to reduce symptoms of anxiety and stress and to attenuate amnesia in geriatric patients.	[40,46, 60]

Table 2. shows some polyherbal formulations used in traditional medicine for management of AD.

Table 2. Polyherbal formulations used in the management of AD

Polyherbal formulation	Composition	Traditional uses	References
Yokukansan	<i>Atractylodis lancea</i> Rhizoma, <i>Poria</i> , <i>Cnidii</i> rhizome, <i>Uncariae Uncis</i> Cum <i>Ramulus</i> , <i>Angelicae Radix</i> , <i>Bupleuri Radix</i> , <i>Glycyrrhizae Radix</i>	YKS is a traditional Japanese medicine approved by the Ministry of Health, Labor and Welfare of Japan. YKS is beneficial for the treatment of behavioral and psychological symptoms of dementia BPSD.	[61,62,63]
Samjunghwan	<i>Mori Fructus</i> , <i>Lycii Radicis Cortex</i> , <i>Atractylodis Rhizoma Alba</i>	SJH has been clinically applied to neurodegenerative disorders as an anti-aging agent.	[64]
Bu-Wang-San	<i>Panax ginseng</i> C.A.Mey, <i>Acorus gramineus</i> Soland, <i>Poria cocos</i> (Schw.) Wolf, <i>Polygala tenuifolia</i> Willd	BWS is a classical Chinese herbal formula, has been used to treat the postmenopausal cognitive disorder for years in clinic.	[65]
Prescription number 1	Composed of more than 20 kinds of Chinese medicines, in which the main herbs used are <i>Radix astragali</i> , <i>Radix codonopsis</i> , <i>Rhizoma atractylodis</i> , <i>Macrocephalae</i> , and <i>Cistanches herba</i>	Clinical application is to treat cerebellar atrophy, dystaxia, and cerebral palsy with minor side effects. PN-1 is also useful in improving memory of the elderly in the case of senile dementia.	[66]
Jangwonhwan	Consists of a decoction of 12 medicinal plants and mushroom, including red <i>Panax ginseng</i> C.A. Meyer and white <i>Poria cocos</i> (Schw.) Wolf (family: Polyporaceae)	It is an oriental medicine that has historically been administered to patients with amnesia.	[67]

2.5. Physical Exercise in Patients with AD

Existing hypotheses suggest that physical exercise represents a potential adjunctive treatment for cognitive impairment, which may help to delay the onset of neurodegenerative processes [68]. Although there is limited data on the benefits of exercise in AD, compelling animal data suggests that exercise may have disease-modifying benefits in AD. Exercise appears to stimulate neurogenesis, enhance neuronal survival, increase resistance to brain insults and increase synaptic plasticity [69]. Voluntary exercise may mediate the amyloid cascade in favor of reduced production of β -amyloid. Cross-sectional evidence shows that higher VO_2 peak (a consensually valid measure of aerobic fitness) is associated with less brain atrophy and slower dementia progression in early-stage AD [69].

In individuals 65 years and older, physical activity has been shown to protect against the continuous development of AD. In addition, regular moderate physical exercise can positively influence depressive symptoms in AD patients [68]. It has been found out that swimming training improved learning, and both short- and long-term memory [70]. Moreover, one study concluded that a minimum of one hour per week of walking is beneficial to cognitive function in those with mild-to-moderate AD, suggesting that the walking activities may be one intervening strategy that could be useful in AD populations [71].

In the Canadian Study of Health and Aging, individuals aged 65 years or older who were engaged in regular physical activities had a 50% reduced risk of developing AD [70,72].

Notably, however, this association was much stronger for women than for men. This study also revealed a dose-response effect, indicating that higher reported levels of physical activity were associated with lower risk of cognitive impairment and lower mortality after 5 years [72]. Despite these findings, the benefits of exercise in AD are not well-defined and evidence to develop guidelines for the prescription of exercise in AD is lacking [69].

2.6. Acupuncture

Acupuncture is one of the popular CAM used for treating dementia even though existing evidence does not demonstrate the effectiveness of acupuncture for AD [73]. In Taiwan, acupuncture is commonly used to treat disorders of the nervous system, namely dementia, Parkinson's disease, and epilepsy. A study found that electro-stimulation at specific acupoints increased the activity of certain regions of the brain associated with cognitive functions such as memory and language. Thus the study demonstrated that acupuncture had a beneficial effect in patients with AD [74].

Furthermore, a study on the use of laser acupuncture in animal model of AD demonstrated the cognitive-enhancing effect of laser acupuncture and its positive modulation effect cholinergic function. Therefore, laser acupuncture at HT7 acupoint is a potential non-invasive strategy to attenuate memory impairment [75]. However, due to the limited number of studies on the role of acupuncture in AD patients, it is erroneous to draw any firm conclusions on its beneficial effects [73].

2.7. Dietary Supplements and Nutraceuticals

Dietary supplements, functional foods or nutraceuticals may have preventive and/or therapeutic actions against AD. Several studies indicate that supplementation of vitamins such as folic acid and vitamin B12 significantly reduces homocysteine levels in patients, thus decreasing the possibility of acquiring sporadic forms of AD [76] and a lower rate of cognition decline [77]. However vitamin B supplementation cannot be recommended for the treatment of AD [77].

Functional foods can perform neuroprotective effects through antioxidant actions, which can prevent neuronal death. A higher intake of vegetables, fruits, and seeds rich in vitamin C, carotenoids and vitamin E is positively associated with better cognitive function and a decreased risk of dementia in the elderly [70]. The combination of vitamin E and vitamin C has been reported to reduce the prevalence of AD in aged people [78,79]. An interesting finding is that dietary intake of vitamin E exhibits beneficial effects for neurodegeneration, but supplement doses 10-fold, or even 100-fold, higher than what is obtained by diet show disappointing outcomes against neurodegenerative diseases in most large-scale interventional trials. The neuroprotective effect of vitamin E is believed to be performed by the combination of its different tocopherol forms [78]. A reduced risk of Alzheimer disease in users of antioxidant vitamin supplements was also reported in the Cache County Study [79].

Supplementation of small molecules such as coenzyme Q10 and glutathione can be interesting mitochondrial-directed therapies for AD since they are usually expressed in decreased levels in neurodegenerative diseases. A newly developed vitamin E derivative, namely MitoVit E is under study as a potentially significant therapeutic agent for neurodegenerative diseases. However to date its efficacy is largely unclear [80].

Specific foods have also been recognized as likely contributors to a greater or lower risk of developing AD. For example, high intake of fish is associated with a lower risk of AD due to the high level of omega-3 fatty acids. Omega-3 fatty acids are believed to possess free radical scavenging ability, and to reduce lipid peroxidation amongst other properties [79]. A number of prospective epidemiological studies have shown good correlations between fish and/or n-3 polyunsaturated fatty acids (PUFA) intake and a 60–70% decreased risk of developing AD. The positive correlation of fish or DHA intake with better cognitive function and less risk of developing dementia, would suggest that brain levels of the important constituent, DHA, might be reduced in different types of dementia, including AD. Nevertheless, it should be born in mind that increased dietary DHA only seems to be of benefit for healthy individuals or for persons with mild cognitive impairment. Once Alzheimer's has been diagnosed then it seems too late for a beneficial effect of n-3 PUFAs [81].

Shilajit, a blackish brown substance either in powder form

or an exudate found in rocks in the Himalaya Mountains has been known for centuries in Ayurvedic medicine as a rejuvenating and anti-aging compound. Molecularly, Shilajit consists mainly of humic substances, which are the result of degradation of plants by several microorganisms, especially fungi. This leads to the generation of a phytocomplex rich in humic substances, selenium and fulvic acid which is attributed with the many medicinal properties of Shilajit. A formulation consisting of Shilajit and B complex vitamins has been shown to have neurotrophic effects [76].

A typical Mediterranean diet may be associated with a lower risk of AD. Major components of the Mediterranean diet that are thought to contribute to protection against age-related cognitive decline include high intake of monounsaturated fatty acids, fish, cereals, olive oil and red wine. The high antioxidant content of many of these foods combined with the reduced caloric intake associated with the Mediterranean diet is the proposed explanation for the observed decreased incidence of AD [79]. Higher adherence to the Mediterranean diet is also associated with lower mortality in AD [77].

3. Parkinson's Disease

Parkinson's disease (PD) is the second most common neurodegenerative disorder after Alzheimer's disease. PD occurs worldwide, with equal incidence in both males and females. The prevalence increases exponentially with age between 65 and 90 years. The mean age of onset is about 65 years. However 5-10% of people who develop PD, experience symptoms before the age of 40 (young onset) and juvenile onset is when people experience these symptoms before the age of 20. Patients with PD have a higher mortality risk than individuals without PD and the mortality risk increases with disease duration [82]. PD is mainly characterized by a progressive and massive loss of dopaminergic neurons in the substantia nigra pars compacta (SNc), which leads to several motor symptoms [83]. Motor symptoms of PD involve bradykinesia, rigidity, tremor and postural instability. PD patients also suffer from non-motor symptoms such as disturbances of olfaction, vision, sleep and of the autonomic nervous system. Moreover many PD patients present neuropsychiatric symptoms such as anxiety, fatigue, apathy, anhedonia, depression and dementia [84].

3.1. Pathological Changes in PD

The degeneration and loss of pigmented dopaminergic neurons of the SNc of the basal ganglia on midbrain is recognized to be the principal pathological characteristic of PD. Parkinsonian symptoms start to appear when 50-60% of SNc dopaminergic neurons and 70-80% of striatal nerve terminals are lost. The loss of neurotransmitter systems are likely to account for secondary clinical features in PD that include apathy, anhedonia and depression, cognitive decline, sleep abnormalities, sensory dysfunction with hyposmia (reduction in sense of smell) or pain, autonomic instability,

as well as gastrointestinal and genitourinary disturbances [82].

In addition to the degeneration of dopaminergic neurons in the substantia nigra, cytoplasmic inclusions in residual dopaminergic neurons of the SNc known as Lewy bodies are often observed in the brains of PD patients post-mortem. Formation of intra-neuronal Lewy bodies is a pathologic hallmark of PD and an affirmative post-mortem diagnostic marker. Lewy bodies are commonly observed in the brain regions showing the most neuronal loss in PD, including substantia nigra and locus coeruleus. The major compound of these proteinaceous deposits is aggregated forms of α -synuclein. The formations of abnormal α -synuclein filamentous aggregates implicate this protein in the cellular pathology of PD and other neurodegenerative disorders [82].

The basal ganglia comprise several distinct subcortical interconnected nuclei; the striatum, the globus pallidum, the subthalamic nucleus, the SNc and SN reticulata. The basal ganglia play an important role not only in the control of movements but also in some cognitive and behavioral functions. The basal ganglia participate in a feedback loop which begins at the motor cortex, proceeds through the basal ganglia to the thalamus, and back to the motor cortex. Dopamine (DA) is thought to modulate striatal activity and in turn the flow of cortical information through the basal ganglia. When the dopaminergic inputs to the basal ganglia are lost in PD, increased inhibitory activity from the basal ganglia results in over-inhibition of the thalamocortical and brain stem motor centers which produces poverty and slowness of movement as is seen in the diminished facial expression and difficulty in initiating and then terminating movement [82].

3.2. The Pathogenesis of PD

The molecular pathways leading to these concomitant clinical alterations remain obscure, but it is believed that it may result from environmental factors, genetic causes or a combination of both [83]. There is a growing recognition of the role of inflammation in the brain (neuro-inflammation) in the pathogenesis of PD [82].

Mutations in six genes are now known to cause hereditary Parkinsonism or contribute to an individual's risk of developing PD. These are:

Parkin is an E3 ligase which attaches ubiquitin molecules to defective proteins, tagging them for destruction. Mutations in the parkin gene slow down the destruction of the defective proteins, resulting in abnormal protein accumulation in the cell which leads to nigrostriatal neuronal degeneration [82].

α -Synuclein has a role in regulating membrane stability and neuronal plasticity. It also has antioxidant functions and is involved in DA storage and release. The pathogenesis of PD is thought to involve the abnormal folding, aggregation, and deposition of α -synuclein as key steps in mediating neuronal dysfunction and degeneration. α -Synuclein is a major component of Lewy bodies that are toxic to the

neurons [82].

Ubiquitin C-terminal hydrolase L1 (UCHL1) is a susceptibility gene for PD and a potential target for disease-modifying therapies. It is suggested that the UCH-L1 gene encodes two opposing enzymatic activities that affect α -synuclein degradation and PD susceptibility [82].

DJ-1 protein appears to be involved in cellular responses against oxidative stress. Over-oxidation of DJ-1 with age and exposure to oxidative toxins may lead to inactivation of DJ-1 function, suggesting a role in susceptibility to sporadic PD and may also promote α -synuclein aggregation and the related toxicity [82].

PINK1 (PARK6) mutations have been linked to recessively inherit early onset Parkinsonism and appear to be the second-most-common genetic cause in autosomal recessive PD [82].

LRRK2 (Leucine rich repeat kinase 2) gene appears to play a major role in protein-protein interactions like signal transduction and in assembly of cytoskeleton. LRRK2 are detected in Lewy bodies in brains of patients affected by PD and dementia with Lewy bodies, and therefore might be involved in Lewy body formation and disease pathogenesis [82].

3.3. Environmental Factors and PD

Environmental factors along with gene-environmental interactions play a significant role in the development of idiopathic PD. One line of evidence involves the L-dopa responsive, acute parkinsonian syndrome which was reported in young drug abusers after repeated intravenous administration of an impure preparation of 1-methyl-4-phenyl-4-propionoxypiperidine (MPPP). Several years later, neuropathological examination revealed moderate to severe depletion of pigmented nerve cells in the SNc. Secondly, recent epidemiological studies suggest that exposure to pesticides, such as rotenone, paraquat or maneb, may contribute to the higher incidence of sporadic Parkinsonism among the population of rural areas [82].

3.4. Pharmacological Treatment of PD

Drug treatment is started when motor symptoms cause functional disability and to provide symptomatic relief, reduce disability, maintain independent functioning and thus improving quality of life of the patient. Currently initial therapy includes L-dopa, dopaminergic agonists, monoamine oxidase B inhibitors and drug combinations. Other medications include catechol-O-methyltransferase, anticholinergic agents and amantadine [82].

3.4.1. Levodopa

Therapy usually begins with L-dopa which aims to correct the deficit in DA production resulting from the degeneration of dopaminergic nigral neurons. Levodopa is the immediate precursor of DA and is converted into DA through decarboxylation in the brain and in peripheral tissues. It is

combined with carbidopa to block some peripheral conversion, thereby preventing nausea and permitting more of the drug to reach the brain [82].

3.4.2. Dopamine Agonists

Dopamine agonists have the advantage of inducing fewer motor complications such as wearing off, dyskinesias, and on-off motor fluctuations, which might be due to a more continuous stimulation of dopamine receptors as a result of the longer half-life of the dopamine agonists compared with L-dopa. The most common side effects with all dopamine agonists are dizziness, postural hypotension, nausea, vomiting, dyspepsia and peripheral edema [82].

3.4.3. Monoamine Oxidase B Inhibitors

These agents block the enzyme MAO-B that converts DA to DOPAC, leading to an increase in DA levels in the synaptic cleft. Though symptomatic benefits are modest, they are being increasingly used for early PD in relatively young patients, for they might delay the onset of motor fluctuations, at least during the first 5 years of treatment [82].

3.4.4. Catechol-O-Methyltransferase Inhibitors (COMT)

The COMT inhibitors tolcapone and entacapone prolong the half-life of L-dopa preparations by 30% to 50% by reducing L-dopa catabolism. The COMT inhibitors are being used as an adjunct to L-dopa for the treatment of patients with PD with motor fluctuations. Liver function should be monitored frequently since tolcapone is associated with severe hepatotoxicity. Adverse effects may include dystonia, nausea, abdominal pain, diarrhea, sleep disturbances, hypotension, and hallucinations [82].

3.4.5. Amantadine

Amantadine hydrochloride is a tricyclic amine, developed as an antiviral to treat influenza A and was found to ameliorate symptoms in a patient with PD. The mechanisms of action of the antiparkinsonian effects of amantadine are not fully elucidated but the drug has been shown to act pre-synaptically, enhancing the release of dopamine and inhibiting its reuptake and post-synaptically. In some elderly patients, amantadine can cause depression, irritability, or anxiety, but these side effects can be managed by reducing the starting dose [82].

3.4.6. Anticholinergic Drugs

The belladonna alkaloids e.g., atropine and scopolamine were the first agents used in the treatment of Parkinsonism whose aim was to correct the imbalance between DA and acetylcholine levels by blocking muscarinic receptors in the striatum. Side effects of this class of drugs are those of antimuscarinic actions e.g., dry mouth, blurring of vision, urinary retention, memory impairment and constipation [82].

3.4.7. Remacemide

Remacemide, a low affinity, non-competitive N-methyl-D-aspartate receptor antagonist, may be effective in

improving symptoms without exacerbating L-dopa-induced dyskinesia. The most common adverse events are nausea, vomiting, dizziness, headache, abnormal vision, and hypokinesia [82].

3.5. Complementary and Alternative Medicines for PD

Treatment of PD does not involve only appropriate drug therapy but also counseling, allied health intervention and, normally, management of cognitive and psychiatric co-morbidity. The chronic and debilitating symptoms of PD mean that patients often turn to complementary medicine for their alleviation. Furthermore the high amount of side-effects of the conventional treatment favors the use of CAM therapy. Exercise and physiotherapy is often recommended for managing PD and there is some evidence of their effectiveness. Regular movement has a measurable effect on the signs and symptoms of the disease as well as on its progression. It has been claimed that physical activity can help protect dopamine-producing cell from early death. Exercise limits motor impairments and helps to maintain brain DA levels [85].

3.5.1. Acupuncture

Acupuncture has been used to relieve PD-like symptoms in Asian countries for centuries and it has been demonstrated to possess neurotrophic and neuroprotective effects. Studies involving acupuncture in combination with Yin Tui Na massage was found to significantly improve scores on the Unified Parkinson's Disease Rating Scale (UPDRS) after treatment. Acupuncture applied to body or scalp acupoints result in improvements in sleep and rest only. Acupuncture has also been seen to improve blood flow and glucose metabolism in brain tissue in patients with the disease, suggesting that acupuncture does play a beneficial role in delaying intellectual decline in patients with PD [74].

Bee venom acupuncture (BVA), which involves the injection of dilute bee venom into acupuncture points, is used in the treatment of disorders such as pain, arthritis, rheumatoid diseases, cancer, and skin diseases. The anti-neuroinflammatory effect of bee venom has been investigated, and the possibility of its use in the treatment of neurodegenerative disorders was found that bee venom effectively protected dopaminergic neurons against neurotoxin MPTP (1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine). It was showed that there was significant improvement in motor symptoms and total UPDRS score. However the mechanism underlying the effects of acupuncture on motor symptoms in PD is unclear [86].

Retained acupuncture was reported to attenuate MPTP-induced neuronal damage in mice. Accumulating evidence suggests that many neurotransmitters such as endorphins, serotonin, 5-hydroxytryptamine (5-HT), epinephrine, cholecystokinin and others are mobilized by peripheral acupuncture stimulation. Although evidence of acupuncture's effectiveness in humans remains lacking,

some studies have suggested that electroacupuncture (EA) is beneficial when treating a neurological deficit in PD animals. It has been reported that 5-HT suppresses the dopaminergic pathway and there is evidence that EA induces the activation of 5-HT-containing neurons subsequently suppresses central dopaminergic neural transmission [87].

3.5.2. Massage (Tactile Touch)

Massage therapy is older than recorded time, and rubbing was one of the primary forms of medicine until the pharmaceutical revolution. However, Tactile Touch (a superficial touch technique) still remains to be evaluated. In a study on the effect of Tactile Touch (TT) on sleep and pain in PD, there was a more prominent decrease of pain in the short term follow up with the emotional and physical expressions of pain being reduced significantly. There was significant improvement in the frequency of early awakenings and increased in undisturbed sleep from 2 to 3 hours during the study time. However no effects were seen on daytime tiredness, difficulties in falling asleep or the frequency of nightly urination, painful cramps or nightly numbness. Thus a positive effect on sleep is seen with TT [88].

3.5.3. Tai chi

Tai chi is a form of complementary medicine with similarities to aerobic exercise. It combines deep breathing and relaxation with slow and gentle movements. Tai chi has been reported to have beneficial effects in reducing high blood pressure, and improving balance, muscle strength and fall prevention. One reason for using tai chi for treating PD is that it is claimed to be effective at improving flexibility and balance as well as reducing the frequency of falls [85]. It was also found to be a safe therapy and effective in improving postural stability and reduced dyskinesia in patients with mild-to-moderate PD. Thus, clinically these changes indicate increased prospective for effectively performing daily life functions, such as reaching forward to take objects from a cabinet, transitioning from a seated to a standing position (and from standing to seated), and walking, while reducing the probability of falls. The improvements in gait characteristics support the efficacy of tai chi in alleviating the bradykinetic movements associated with PD [89]. However another study reported that tai chi had no effect on locomotor ability and the motor performance did not differ between tai chi and no treatment and finally tai chi did improve functional fitness but not UPDRS score or depression. Possible mechanisms of action of tai chi may include normalizing neurotransmitter levels such as DA or by improving muscle flexibility and trunk rotation. Furthermore, tai chi may help promoting attentional resources in the basal ganglia by its meditative effects altering the reticular formation output. Daily repetitive practice of tai chi may also promote development of new neural pathways, new motor programs, allow faster reactions when responding to postural challenges [85].

3.5.4. Yoga

A study involving a 57-year old male showed that after an intervention of 6 months yoga sessions, there were improvements in muscle length in almost all areas such as shoulders, hip and knee flexors, extensors and adductors. These improvements were expected since research has found stretching and yoga can significantly increase flexibility which is desirable since rigidity is a common clinical manifestation in those with PD. Substantial gains were made in muscle strength in almost all muscle groups. Muscle weakness in PD is a complex problem that may stem from multiple factors including centrally induced neural drive, diminished muscle force secondary to diminished movement velocity and the peripheral loss of muscle function from disuse and the aging process. Evidence suggests that improving muscle strength is important for people with PD to preserve and enhance overall quality of life and functional mobility. Improvements in reaction time were enough to place him in the normal range for someone his age and may be attributed to the extensive use of agility exercises. Faster reaction times are important for people with PD since bradykinesia affects voluntary and reactive limits of stability, and increasing the speed of self-initiated movement can help lessen the effects of bradykinesia [90].

3.5.5. Reflexology

Reflexology involves using a series of pressure techniques to stimulate specific reflex areas on the feet and hand with the specific intention of invoking a beneficial response in other parts of the body. Therefore it is a method of activating the healings powers of the body, notably balancing the whole body, reduction of stress and deep relaxation. A study showed that after 20 weeks of therapy people improved overall in the domains of activities of daily living, emotional well-being and cognitive impairment but deteriorated in the remaining domains such as mobility, stigma, social support, communication and bodily discomfort. The most immediate benefit of reflexology for recipients is relaxation [91].

3.5.6. Music

Music (MT) as CAM therapy is well known. The use of music as an adjuvant to the control of pain, especially during medical procedures has been studied. In PD, one form of MT that was studied involved the effects of choral singing, voice exercise, rhythmic and free body movements. It was found that a significant overall positive effect on bradykinesia as measured by the UPDRS. MT was also helpful to improve and, at times, restore many functions, including motor capacities in PD [88].

3.5.7. Aromatherapy

Aromatherapy is a practice that uses essential oils from plants that are particularly suited to the person. They are massaged on the skin, put into bath or simply smelled. The overall effect of the therapy can be an intense and most agreeable relaxation. Thus, it can be useful in treatment of

the neuropsychiatric symptoms of PD [92].

3.5.8. Coenzyme Q10

Excessive production of ROS is a hallmark of disease progression in PD pathophysiology. Coenzyme Q10 is an especially relevant antioxidant in PD research, because it also facilitates function of the mitochondrial transport chain (MTC). Exogenously administered CoQ10 has been shown to restore electron transport chain activity in In-vitro studies using fibroblasts from PD patients. As a lipophilic antioxidant, CoQ10 is capable of scavenging radicals within membranes and in the cytosol and plasma when bound to lipoproteins. Its ubiquitous presence throughout cytosol, membranes, and plasma earned it the name ubiquinone. Preliminary data from a phase I study suggested that that exogenously administered CoQ10 may retard disease progression in PD. Platelet CoQ10 redox ratios have been shown to be significantly decreased in PD patients [93].

3.5.9. Vitamin E

Experimental evidence has illustrated that oxidative stress is responsible for damage in the substantia nigra and subsequent PD development. Vitamin E is known to protect against oxidative damage, due to its antioxidants properties and may be used in the prevention and/or treatment of PD. It was shown that vitamin E deficiency increased MPTP toxicity in the MPTP-induced PD mouse model. It was also studied that high-dose α -tocopherol, in association with ascorbic acid, may delay the progression of PD by an average of 2.5 years. Furthermore it was also reported that a diet rich in vitamin E reduces the risk of developing PD [94].

3.5.10. Traditional Chinese Medicine (TCM)

In traditional Chinese medicine (TCM), PD is termed as “shaking palsy”, a syndrome characterized by tremors, numbness and limpness and weakness of the four limbs. According to the theories of TCM, the key pathological features of PD include: stagnancy of *Qi* (energy) and blood stasis, deficiency of liver- *Yin* and kidney-*Yin*, and deficiency of both *Qi* and blood [95]. TCM has played an important role in the medical care of PD patients for thousands of years in China and is still widely used with its application covering about three-fourths of the areas in China as well as in Asian countries such as Korea and Japan [96, 97].

“*Jia Wei Liu Jun Zi Tang*” (*JWLJZT*) is an ancient formulation developed by a TCM doctor *Zhang Lu* in 1695 AD, with the specific function of tonifying the energy (*Qi*) of spleen and stomach and used to treat symptoms of PD. Based on the original recipe for *JWLJZT*, the herbal preparation contained 11 herbs as given below:(table3)

JWLJZT made from a Chinese herbal decoction, significantly reduced some non-motor complications in patients with PD under conventional medicine treatment. The major improvement was reflected by the reduction of score in UPDRS IVC which assessed gastrointestinal disorders, such as anorexia, nausea and vomiting, sleep disturbances, such as insomnia and hypersomnolence, and symptomatic orthostasis. However *JWLJZT* had no effect on Parkinsonian motor abnormality [97].

Table 3. Composition of the herbal preparation *JWLJZT*

Chinese name	Pharmaceutical name
<i>Dang shen</i>	Dried root of <i>Codonopsis pilosula</i> (Franch.) Nannf. (Fam. Campanulaceae)
<i>Sheng di</i>	Dried root tuber of <i>Rehmannia glutinosa</i> Libosch. (Fam. Scrophulariaceae)
<i>Fu ling</i>	Dried sclerotium of the fungus, <i>Poria cocos</i> (Schw.)Wolf. (Fam. Polyporaceae)
<i>Gou teng</i>	Dried hook-bearing stem branch of <i>Uncaria rhynchophylla</i> (Miq.) Jacks. (Fam. Rubiaceae)
<i>Bai Zhu</i>	Rhizome of <i>Atractylodes macrocephala</i> Koidz. (Fam. Compositae)
<i>Dang gui</i>	Dried root of <i>Angelica sinensis</i> (Oliv) Diels. (Fam. Umbelliferae)
<i>Fa ban xia</i>	Dried tuber of <i>Pinelliae ternate</i> (Thunb.) Breit. (Fam. Araceae)
<i>Chuan xiong</i>	Dried rhizome of <i>Ligusticum chuanxiong</i> Hort. (Fam. Umbelliferae)
<i>Huai niu xi</i>	Dried root of <i>Achyranthes bidentata</i> Bl. (Fam. Amaranthaceae)
<i>Chen pi</i>	Dried pericarp of the ripe fruit of <i>Citrus reticulata</i> Blanco. (Fam. Rutaceae)
<i>Sheng gan cao</i>	Dried root and rhizome of <i>Glycyrrhiza uralensis</i> Fisch. (Fam. Leguminosae)

“Zhenzhanning” (ZZN), another herbal medicine used against PD was assessed for its efficacy and was reported that frequency of nausea, vomiting, anorexia and orthostatic hypotension of the test group decreased significantly more than in the control group. Moreover other clinical experiments with Chinese herbal medicines have demonstrated significant improvement in non-motor complications of conventional therapy, including reduced sleeplessness, vivid dreaming, constipation, dizziness and fatigue [97].

3.5.11. Ayurveda

Ayurveda, the traditional system of medicine practiced in India can be traced back to 6000 BC [98]. Ayurveda occupies an important place in health care as an alternative system in India. Even in other neighboring countries in Asia including Nepal, Tibet, Sri Lanka, Burma, Malaysia and Indonesia, the Ayurvedic system effectively supplements the allopathic (modern medicine) system of medicine [99]. In Ayurveda, “Kampavata” is the term used to explain Parkinson’s syndrome [95]. Parkinson’s disease Ayurveda treatment aims at balancing disturbed vata [100]. General treatment of PD in Ayurveda include judicious combination of oral ingestion of medicated edible fats, sudation, medicated enemas, massage with medicated oil, laxatives, and nasal instillation of medicated solutions. Some of the important plant drugs used is Aswagandha (root of *Withania somnifera*), Atmagupta (seed of *Mucuna pruriens*), Bala (root of *Sida cordifolia*) and Paraseekayavane (dry fruit of *Hyocymus reticulatus*) [95].

A concoction in cow’s milk of a powdered mixture of *Mucuna pruriens* and *Hyoscyamus reticulatus* seeds with *Withania somnifera* and *Sida cordifolia* roots are prescribed for PD in India. It was showed that symptomatic improvement on stiffness, tremor, bradykinesia and cramp-like pain of lower limbs with this concoction in a study. *Mucuna pruriens* is the plant with most evidences of antiparkinsonian effects investigated by several methodologies [101]. *Mucuna pruriens* (cowhage) was used in Ayurvedic medicine to treat PD and mucuna seed preparations are in contemporary use for the treatment of PD in India. Clinical trials showed positive effects of seed powder formulation of *Mucuna pruriens* on PD patients with rapid onset of action and longer on time but without concomitant increase in dyskinesias. Commercial preparations of *Mucuna pruriens* are also available for the treatment of PD [95].

Withania somnifera (Ashwagandha) is very revered herb of the Indian Ayurvedic system of medicine as a Rasayana (tonic). Ashwagandha is commonly available as a churna, a fine sieved powder that can be mixed with water, ghee (clarified butter) or honey. Ashwagandha has been described as a nervine tonic in Ayurveda and is a common ingredient of Ayurvedic tonic. Studies have shown that Ashwagandha slows, stops, reverses or removes neuritic atrophy and synaptic loss and thus can be used against Alzheimer’s, Parkinson’s, Huntington’s and other neurodegenerative

diseases. Pretreatment with Ashwagandha extract was found to prevent all the changes in antioxidant enzyme activities, catecholamine content, dopaminergic D2 receptor binding and tyrosine hydroxylase expression induced by 6-hydroxydopamine (6-OHDA) in rats in a dose-dependent manner. Thus, these results suggest that Ashwagandha may be helpful in protecting the neuronal injury in Parkinson’s disease [98].

3.5.12. Herbal Formulations

In recent years, increasing interest has been devoted to the treatment or prevention of PD by herbal medicines. Recent studies have indicated that a part of active compounds extracted from herbal medicines, herbal extracts and herbal formulations have effects on PD models In vitro and In vivo [102].

Vicia faba, a plant with levodopa content was studied and was showed that *Vicia faba* seeds ingestion produced an increase in the levodopa plasma levels, which correlates with motor performance improvements and a high phenolic content with antioxidant properties. Some reports have revealed that polyphenol flavonoids may be neuroprotective in neuronal primary cell cultures. The polyphenol flavanol epicatechin was shown to attenuate the neurotoxicity induced by oxidized low-density lipoprotein in mouse-derived striatal neurons. *Ginkgo biloba* leaves extract, also known to be rich in flavonoids, protected hippocampal neurons from neurotoxicity induced by nitric oxide or beta-amyloid-derived peptide. The green tea extract and (-)-epigallocatechin-3-gallate also showed neuroprotective effects in N-MPTP model of PD in mice. In addition, tea extract have been previously reported to possess potent antioxidant-radical scavenging activities. Green tea and black tea extracts attenuated the neuronal apoptosis induced by 6-OHDA. TCM is another source of herbal preparations with possible neuroprotective properties. Schisabhenol and Salvianolic Acid A are antioxidants isolated from Chinese herbs that protect cerebral cells from injuries induced by oxidative stress. The extract of the Chinese herb *Tripterygium wilfordii* promotes axonal elongation and protects dopaminergic neurons from the lesion induced by MPP+ and increased the survival of dopaminergic neurons in the substantia nigra pars compacta [101].

Acanthopanax senticosus Harms

Acanthopanax Senticosi Radix Et Rhizoma Seu Caulis is the dried roots and rhizomes of *Acanthopanax senticosus* (Rupr. Et Maxim.) Harms. (Araliaceae). Its ethanolic extract has protective effects on dopaminergic neurons in PD mice model induced by MPTP-HCl. The stem bark of *Acanthopanax senticosus* Harms is also effective on PD model *in vivo* and increase the level of DA and noradrenaline (NA) in PD rat model. The components of *Acanthopanax senticosus* Harms contain sesamin and eleutheroside B, etc. Sesamin has a preventive effect on behavioral dysfunction in rotenone-induced rat. Sesamin modulates tyrosine hydroxylase (TH), superoxide dismutase, catalase (CAT),

inducible nitric oxide synthase (iNOS) and interleukin-6 expression in dopaminergic cells under MPP⁺-induced oxidative stress. Eleutheroside B can increase extracellular regulated protein kinases 1/2 phosphorylation and reduce c-fos and c-jun expressions in MPP⁺-induced PC12 cells [103].

Camellia sinensis

Green tea is the product derived from the leaves of *Camellia sinensis* (L.) O. Kuntze (Theaceae). A recent study pointed out that the intake of Chinese and Japanese teas such as oolong tea and green tea can reduce risk of PD. Green tea extracts can attenuate 6-OHDA-induced nuclear factor- κ B (NF- κ B) activation and cell death in SH-SY5Y cells. Polyphenolic catechins derived from green tea have protective effects on the SH-SY5Y cells and the rat model of PD through inhibition of ROS–nitrogen monoxide (NO) pathway. The four main components of polyphenolic catechins are (–)-epigallocatechin-3-gallate, (–)-epicatechin gallate, (–)-epigallocatechin, and (–)-epicatechin. (–)-Epigallocatechin-3-gallate regulate dopamine transporter internalization via protein kinase C-dependent pathway in MPP⁺-induced PC12 cells, reduces dichlorodiphenyltrichloroethane- induced cell death in dopaminergic SHSY-5Y cells. *In vitro*, (–)-epigallocatechin-3-gallate can also inhibit iNOS expression and cell death in the MPTP mice of PD [101].

Cassia obtusifolia

Cassiae Semen is the dried, ripe seed of *Cassia obtusifolia* L. or *Cassia tora* L. (Leguminosae). The ethanolic extract has effects against neurotoxicities induced by 6-OHDA in PC12 cells, and significantly protects DA neuronal degeneration induced by MPTP in the mouse PD model. Alaternin isolated from *Cassia tora* has a potent Peroxynitrite(ONOO⁻)-scavenging and anti-inflammatory activities and can be a candidate for PD treatment as ONOO⁻-toxicity which is reported to be involved in inflammatory and neurodegenerative diseases [101].

***Centella asiatica* (L.)**

Centella asiatica (L.) Urban is a tropical medicinal plant from Apiaceae family native to Southeast Asian countries such as India, Sri Lanka, China, Indonesia, and Malaysia as well as South Africa and Madagascar. It has a long history of utilization in Ayurveda and Chinese traditional medicines since centuries as well as being cultivated successfully due to its medical importance in some countries including Turkey. Monographs of the plant describing mainly its wound healing and memory enhancement effects exist in the European Pharmacopeia, Commission E of the German Ministry of Health, and World Health Organization (WHO). In addition to neuroprotective effect of *C. asiatica*, it has been reported to own a wide range of biological activities desired for human health such as wound healing, anti-inflammatory, antipsoriatic, antiulcer, hepatoprotective, anticonvulsant, sedative, immunostimulant, cardioprotective, antidiabetic, cytotoxic and antitumor, antiviral, antibacterial,

insecticidal, antifungal, antioxidant, and for lepra and venous deficiency treatments. The positive effects of *Centella asiatica* on brain aging have been generally attributed to its two major triterpene saponosides; asiatic and madecassic acids as well as their heterosides; asiaticoside and madecassoside, respectively. TYRO has become an important target for PD since this enzyme plays a role in neuromelanin formation in the human brain and could be significant in occurrence of dopamine neurotoxicity associated with neurodegeneration linked to PD and results have shown that ethanolic extracts of the plant show notable TYRO inhibition. Therefore it can be concluded that *C. asiatica* extract might be beneficial in prevention of neuronal damage [101].

***Gastrodia elata* Blume**

Gastrodiae Rhizoma is the dried tuber of *Gastrodia elata* Bl. (Orchidaceae) with its ethanolic extract having protective effects on MPP⁺-induced cytotoxicity in human dopaminergic SH-SY5Y cells. Vanillyl alcohol, a major bioactive component of *Gastrodiae Rhizoma*, protects dopaminergic MN9D cells against MPP⁺-induced apoptosis by relieving oxidative stress and modulating the apoptotic process and is therefore a potential candidate for treatment of neurodegenerative diseases such as PD [102]. The phenolic glucoside gastrodin is an active constituent of *Gastrodia elata* Blume and is one of the most important traditional plants in Oriental countries. Gastrodin has been used to treat various ailments such as headache, dizziness, vertigo, and convulsive illnesses in traditional medicine. Furthermore scientific reports support the antioxidative, anticonvulsive, anti-inflammatory, antiepileptic, antiobesity, anxiolytic, and learning and memory improvements in activities of gastrodin. Moreover gastrodin significantly attenuates the expression levels of neurotoxic proinflammatory mediators including inducible nitric oxide synthase, cyclooxygenase-2, and the proinflammatory cytokines tumor necrosis factor- α and interleukin-1 β in lipopolysaccharide-stimulated microglial cells. Gastrodin is also a potent antioxidant and free radical scavenger that decreases the levels of lipid peroxidation and increases the expression of genes encoding antioxidant proteins. In addition, gastrodin has been used in clinics as an effective and safe drug for preventing neurocognitive decline following cardiopulmonary bypass and is beneficial to older patients with refractory hypertension by improving the balance of endothelin and nitric oxide in plasma, suggesting safe use in humans. It was reported that gastrodin possessed neuroprotective effects in *In vitro* and *In vivo* PD models possibly by inhibiting oxidative stress and apoptosis-induced neuronal cell death. Gastrodin has a powerful antioxidant with significant radical scavenging activity for DPPH and alkyl radicals. Moreover, gastrodin pretreatment significantly reduce the level of intracellular ROS in SHSY5Y cell treated with MPP⁺ and an increase in superoxide dismutase (SOD) activities was observed with the elimination of hydrogen peroxide, free radicals and superoxide anion in the brain. Gastrodin effectively attenuated MPTP-induced PARP

cleavage indicating that its protective effect associated with inhibiting downstream apoptotic signaling pathways, which prevented PARP proteolysis. Moreover, gastrodin can cross the blood-brain barrier, enter the central nervous system, and protect against nerve lesions [104].

Hypericum perforatum L.

Hyperici Perforati Herba is the dried aerial part of *Hypericum perforatum L.* (Guttiferae). The methanol extract of the plant has neuro-modulating effect against MPTP-induced PD in mice.

The standard extracts of *Hypericum perforatum L.* have

neuroprotective effects on trauma induced by H₂O₂ in PC12 cells, and reduce oxidative stress and increase gene expression of antioxidant enzymes on rotenone-exposed rats. A flavonoid-rich extract of *Hypericum perforatum L.* has protective effects against H₂O₂-induced apoptosis in PC12 cells. Hyperoside isolated from *Hypericum perforatum L.* has protective effects against cytotoxicity induced by H₂O₂ and tert-butyl hydroperoxide in PC12 cells [95].

Table 4 below shows other plants with potential to be used in PD treatment:

Table 4. Plants with potential to be used for treatment of PD

Plant species and family	Extract and compound and their main biological properties	Refs
<i>Allium sativum L.</i> Liliaceae	S-allylcysteine : Preventing loss of DA cells, antioxidant <i>in vivo</i>	[95]
<i>Alpinia oxyphylla</i> Miq. Zingiberaceae	Ethanol extract: Antioxidant, anti -inflammation <i>in vivo</i> PCA: Antioxidant, anti-apoptosis, mitochondrial protection <i>in vitro</i>	[95]
<i>Bacopa monnieri</i> (L.) Wettst. Scrophulariaceae	Standardized powder: Antioxidant, inhibiting DA Depletion <i>in vivo</i>	[95]
<i>Chaenomeles speciosa</i> (Sweet) Nakai Rosaceae	Water extract: DAT inhibitor both <i>in vivo</i> and <i>in vitro</i>	[95]
<i>Chrysanthemum morifolium</i> (Ramat.) Tzvel. Compositae	Water extract : Antioxidant, anti-apoptosis <i>in vitro</i>	[95]
<i>Cistanche salsa</i> (C. A. Mey.) G. Beck Orobanchaceae	Acteoside: Anti-apoptosis <i>in vitro</i> Echinacoside : Inhibiting DA depletion, anti-apoptosis in both <i>in vitro</i> and <i>in vivo</i> PhGs: Inducer of NTFs, anti-apoptosis <i>in vitro</i> and inhibiting DA depletion <i>in vivo</i> Tubuloside B: Antioxidant <i>in vitro</i>	[95]
<i>Dendrobium nobile</i> Lindl. Orchidaceae	Chrysotoxine : Antioxidant, anti-apoptosis, mitochondrial protection <i>in vitro</i>	[95]
<i>Fraxinus excelsior</i> Linn. Oleaceae	Fraxetin : Antioxidant, anti-apoptosis <i>in vitro</i>	[95]
<i>Ginkgo biloba</i> L. Ginkgoaceae	Ginkgolide b: Anti-apoptosis, Ca ²⁺ inhibition <i>in vitro</i> Extract: Antioxidant, inhibiting DA Depletion <i>in vivo</i> GBE 761: Inhibiting DA depletion, antioxidant, MAO-B inhibition, regulation of copper homeostasis <i>in vivo</i>	[95]
<i>Hibiscus asper</i> Hook.f. Malvaceae	Methanolic extract: Antioxidant, inhibiting depression and spatial memory deficits <i>in vivo</i>	[95]
<i>Kaempferia galangal</i> L. Zingiberaceae	Kaempferol: Autophagic enhancer <i>In vitro</i> and antioxidant <i>in vivo</i>	[95]
<i>Magnolia officinalis</i> Rehd. et Wils. Magnoliaceae	Magnolol : Preventing loss of DA cells <i>in vivo</i>	[95]
<i>Myrtus communis</i> L. Myrtaceae	Myricetin : Inhibiting DA depletion, suppressing iron toxicity <i>in vivo</i> and antioxidant, anti-apoptosis, inhibition of MKK4 and JNK <i>in vitro</i>	[95]
<i>Paeonia lactiflora</i> Pall. Ranunculaceae	Paeoniflorin: Activation of adenosine A1 Receptor and alleviating the neurological impairment <i>in vivo</i> and modulating autophagy <i>in vitro</i>	[95]
<i>Panax ginseng</i> C. A. Mey. Araliaceae	G115: Preventing loss of DA cells <i>in vivo</i> Ginsenoside Rg1: Anti-apoptosis, ↓JNK, ↓iron levels, regulating DMT1 and FP1, ↓DMT1 + IRE, ↓ROS-NF-κB, anti-apoptosis, ↑Akt, glucocorticoid receptor, activation of IGF-IR and ER, promoting neurite growth, ER-dependent HO-1 induction, Gbeta1/PI3K/Akt-Nrf2. Ginsenoside Re: Anti-apoptosis, ↓iNOS, inducing neurite outgrowths. Ginsenoside Rh1 & Rg: Inducing neurite outgrowths, ↓ ERK1/2. Water extract: Anti-apoptosis	[95]
<i>Polygala tenuifolia</i> Willd. Polygalaceae	Tenuigenin: Anti-apoptosis, mitochondrial protection <i>in vitro</i> Water extract : Antioxidant and anti-apoptosis both <i>in vitro</i> and <i>in vivo</i>	[95]
<i>Polygonum cuspidatum</i> Sieb. et Zucc. Polygonaceae	Resveratrol: Antioxidant, anti-apoptosis, anti-inflammatory (↓COX-2, ↓TNF-α), provide protection against loss of dopaminergic neurons induced by 6-OHDA and MPTP, inhibiting DA Depletion, autophagy induction (AMPK/SIRT1 pathway) both <i>in vivo</i> and <i>in vitro</i>	[95]
<i>Psoralea corylifolia</i> L. Leguminosae	Δ ³ ,2-hydroxybakuchiol: Inhibiting monoamine transporters both <i>in vitro</i> and <i>in vivo</i>	[95]

<i>Pueraria thomsonii</i> Benth. Fabaceae	Daidzein: Anti-apoptosis <i>in vitro</i> Genestein: Anti-apoptosis <i>in vitro</i> and inhibiting DA depletion, modulating estrogen receptors, antioxidant <i>in vivo</i> Puerarin : Anti-apoptosis, mitochondrial Protection, ↓JNK, regulating the function of UPS, antioxidant <i>in vitro</i>	[95]
<i>Quercus dentate</i> Thunb. Fagaceae	Quercetin: Antioxidant, cognitive-enhancing <i>in vivo</i> , anti-inflammation, ↓iNOS/NO both <i>in vitro</i> and <i>in vivo</i>	[95]
<i>Rhodiola rosea</i> L. Crassulaceae	Salidroside: Antioxidant, ↓nNOS and iNOS, ↓NO <i>in vitro</i>	[95]
<i>Salvia miltiorrhiza</i> Bunge Labiatae	Salvianic acid A: Antioxidant, anti-apoptosis <i>in vitro</i> Salvianolic acid B: Antioxidant, anti-apoptosis <i>in vitro</i>	[95]
<i>Scutellaria baicalensis</i> Georgi Labiatae	Baicalein: Anti-apoptosis, inhibiting DA Depletion, mitochondrial protection, ↓JNK, antioxidant, increasing the levels of DA and 5-HT <i>in vitro</i> and <i>in vivo</i>	[95]
<i>Tripterygium wilfordii</i> Hook. f. Celastraceae	Tripchlorolide: Inhibiting DA depletion, ↑BDNF <i>in vitro</i>	[95]
<i>Withania somnifera</i> (L.) Dunal. Solanaceae	Extract: Antioxidant, inhibiting DA depletion <i>in vivo</i>	[95]
<i>Zingiber officinale</i> Rosc. Zingiberaceae	Eugenol: Antioxidant, inhibiting DA depletion <i>in vivo</i> Zingerone: Antioxidant, inhibiting DA depletion <i>in vivo</i>	[95]

4. Conclusion

Due to the rising prevalence of neurodegenerative diseases among the elderly, there is a pressing need for better treatment in order to alleviate the social and financial burden of these diseases. There are multiple targets for treating Neurodegenerative diseases, which is a complex syndrome. In general, single component just acts on one or a few targets, so it is difficult to control a complex syndrome everlastingly and stably. Herbal formulations contain multiple compounds which contain multiple components, and using herbal medicines or herbal formulations would act on multiple targets and control a complex syndrome well. In the light of this review, we can conclude that there is a plethora of complementary and alternative medicines available for use against neurodegenerative diseases. Hence, in this perspective, CAM especially herbal medicine, can prove to be promising intervening strategies for the treatment and prevention of Alzheimer's and Parkinson's disease.

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