MALAYSIAN JOURNAL OF BIOCHEMISTRY & MOLECULAR BIOLOGY

The Official Publication of The Malaysian Society For Biochemistry & Molecular Biology (MSBMB)
http://mjbmb.org

AN OVERVIEW OF COMPLEMENTARY AND ALTERNATIVE MEDICINE FOR ALZHEIMER'S AND PARKINSON'S DISEASE

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REVIEW ARTICLE

History
Received: 19th May 2021
Accepted: 6th June 2021

Keywords:

Complementary and alternative medicine; Alzheimer's disease; Parkinson's disease

Abstract

Parkinson's disease (PD) and Alzheimer's disease (AD) are two common neurodegenerative diseases that primarily affect the elderly population. AD causes dementia and is associated with disrupted brain structure and function, and its classical hallmarks include the accumulation of the beta-amyloid plaques and build-up of tau tangles. On the other hand, PD features a myriad of motor aberrations characterised by tremors, postural instability, rigidity, and bradykinesia as a result of the loss of dopaminergic neurons in the brain. Currently, available treatment regimens for AD and PD show limited efficacy in alleviating the symptoms or reversing pathogenesis. Inadvertently, several complementary and alternative medicine (CAM) methods have been linked to symptomatic relief for both conditions. These CAM approaches include the utilisation of natural products, nutritional supplements, acupuncture, and exercise. In this review, a repertoire of CAM therapies and their effectiveness in alleviating AD and PD are discussed.

INTRODUCTION

Complementary and alternative medicine (CAM) is defined as medical practices that are not usually considered as conventional methods [1]. It is widely practised in Asia, and countries such as Korea demonstrates a high usage of CAM, with up to 76% of its population known to be CAM users [2]. Even though scientific evidence on the efficacy of CAM is still considerably limited, such therapies have shown great potential in disease management. In general, CAM is most frequently practised among adults suffering from chronic diseases [3, 4]. A number of CAM approaches have been used for neurodegenerative diseases such as Alzheimer's (AD) and Parkinson's disease (PD). Reports have shown that substantial therapeutic benefits are achieved when using CAM treatments, which encompass natural products, acupuncture and exercises [4, 5].

AD causes a significant disruption of normal brain structure and function [6, 7] and is the most common cause of dementia. It contributes to 60-70% of the total cases [8]. Over the past 30 years, AD has arisen as a key public health problem with a significant impact on populations worldwide. It is estimated that a total of 5.3 million Americans suffer from AD [9]. Although the pathogenesis of AD remains unknown, researchers believe that it is a multifactorial disease based on evidence from the pathogenesis and development of AD. Although AD is progressive and the prominent risk factor is advancing age (the majority of AD patients are aged 65 years old and above), it is not a manifestation of physiological aging. Clinical symptoms of AD vary among individuals, the most common being memory loss, difficulty in solving problems, disorientation, poor judgment, apathy, and depression. The hallmarks of AD are the progressive accumulation of the

beta-amyloid (βA) plaques, build-up of tau tangles, and death of neurons, leading to brain atrophy [10]. βA is produced from the processing of the amyloid precursor protein (APP). The cleavage of the precursor protein by β-site APP-cleaving enzyme (BACE1) generates two products: a short soluble amino-terminal portion, namely APPsβ, and a long terminal carboxyl fragment, C99. C99 is further cleaved by γ-secretase to produce APP intracellular domain (AICD) and βA [11]. A recent study suggested that fragments from the processing of APP, such as AICD, may also contribute to the pathogenesis of AD [12].

The clinical symptoms of AD are associated with pathological changes in neurotransmission. For example, dysfunction of the glutamatergic system may lead to neuronal loss and cognitive impairment, while cholinergic dysfunction results in memory deficits [13]. N-methyl-d-aspartate (NMDA) receptors involved in the glutamatergic system are over-activated in AD, leading to excitotoxicity which triggers neuronal cell death and decreased synaptic plasticity [14, 15]. On the other hand, cholinergic neurotransmission, crucial to memory acquisition, was found markedly reduced in AD patients. Degeneration of the cholinergic neurons and declined levels of acetylcholine cause memory impairment in patients [16].

Presently, there are several conventional drugs proven to alleviate AD symptoms through two different mechanisms, cholinesterase inhibition and N-methyl-D-aspartate (NMDA) receptor antagonisation. Donepezil, galantamine, and rivastigmine are cholinesterase inhibitors that work by delaying the breakdown of neurotransmitters. Contrarily, NMDA receptor antagonist such as memantine maintains glutamate activity involved in memory and learning [17]. However, to date, no effective treatment is capable of arresting or even decelerating AD-associated neuronal death [18]. Conventional drugs are encumbered with several limitations such as high cost, short periods of efficacy, and a multitude of side effects. Not only have these drugs not shown promising results; tolerance may arise after a short treatment regimen [19, 20].

On the other hand, PD is characterised by tremors, postural instability, rigidity, and slow movements. The disease generally affects individuals over the age of 60, with a manifestation of early motor symptoms followed by non-motor symptoms, for instance, depression, sleep interference, and cognitive impairment. The pathophysiology or cause of this disease remains unknown, but it is believed that the loss of dopaminergic neurons in the substantia nigra triggers the cascade of symptoms. Besides, Lewy bodies which contain several misfolded proteins including alpha-synuclein, tau and βA may contribute to pathogenesis of the disease [21, 22].

Loss of dopamine results in the reduction of dendritic spine density on medium spiny output neurons [23], which may impact cortico-striatal transmission. In addition, changes in basal ganglia neuron firing rates were associated with loss of dopamine. Dopamine depletion also causes the firing burst in neurons [24, 25]. Under normal conditions, adjacent basal ganglia neurons fire in an uncorrelated pattern. However, under a dopamine-depleted environment, they discharge in a synchronised pattern [26]. The changes associated with dopamine depletion eventually contribute to the motor symptoms of PD.

Unfortunately, to date, there has been no major breakthrough in drug discovery research that may potentially halt the development of the disease. Thus, treatment has been mainly directed at improving the symptoms by dopaminergic therapy. The gold standard treatment for PD is the use of levodopa to alleviate motor symptoms. While it has been proven to be effective in controlling behavioural disorders and motor symptoms [27] as well as restoring some functions in the frontal lobe, long-term use of levodopa treatment is known to result in side effects such as dyskinesia.

Current treatment options are not very effective at stopping or slowing the progression of the diseases. Hence, the quest to alleviate AD and PD remains a huge challenge in medicine. Many patients have now shifted their attention to alternative treatment options such as CAM, motivated by the increasing pool of evidence that showed that CAM can be equally, or at times, better than conventional medicine [28-30]. Therefore, this review aims to provide information on some of the most common CAM approaches for AD and PD, and also to discuss the evidence on the effectiveness of these approaches. By understanding the current evidence of CAM for AD and PD, clinicians and patients are able to weigh the benefits and risks of these practices. Furthermore, a better understanding of CAM would help to drive future research into the development of new therapy that would benefit at-risk populations globally.

THE SHARED AETIOLOGY AND PATHOGENESIS OF ALZHEIMER'S AND PARKINSON'S DISEASE

Although AD and PD have markedly different clinical and pathological features, they have shared on some common aetiologies and pathogenesis [31]. A number of overlapping signs such as extrapyramidal features, nigral pathology and dementia have been found in both AD and PD. Such overlap may reflect a common pathogenic mechanism for the neurodegeneration in the diseases [32].

Presence of protein deposits in brain due to protein-misfolding is one of the common pathologies of the diseases [33]. Accumulation of the misfolded proteins in AD and PD triggers the activation of microglia, the brain-resident mononuclear phagocytes [34]. A common inflammatory mechanism is observed in AD and PD whereby inflammasome complex is activated in peripheral monocytes and microglia, followed by the production of pro-inflammatory cytokines such as interleukin (IL)-1β and IL-18. The NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3) inflammasome is currently the best characterised inflammasome [35]. Likewise, the opening of

Pannexin 1 channels and Connexin 43 hemichannels appears to be involved in the inflammation in various cerebral neuropathies including AD and PD [36]. Besides, the two abnormal proteins in AD and PD, α-synuclein and tau, trigger the disease pathogenesis by oxidative stress and mitochondrial dysfunction [31]. Growing evidence has suggested the critical role of oxidative stress in neuronal cell death [33]. Peroxidation of the membrane lipid bilayer is a major source of cell damage. Moreover, peroxidation of polyunsaturated fatty acids may lead to the formation of aldehydes such as 4-hydroxy 2-nonenal (HNE) which act as the cytotoxic compounds. HNE-protein adducts have been found to be elevated in brain tissues and body fluids of AD and PD [37]. Accumulation of pathogenic proteins due to endo-lysosomal dysfunction may also cause AD and PD [38]. The previous study has suggested that AD and PD share the same retromer-dependent endosomal trafficking, which is involved in sorting and trafficking cargo out of the endosome [39].

The risk of developing AD and PD might be contributed by various gene mutations [31]. A previous study has reported about genetic variation at HLA-DRB5 that is associated with the onset and progression of AD and PD [40]. Other than this, many genes' dysregulations have been reported for both AD and PD. Ramanan and Saikin (2013) have discovered an AD- and PD-associated regulatory network that is centred on the simian virus 40 promoter factor 1 (SP1) and activator protein 1 (AP-1) transcription factors [41]. In a genome-wide association studies (GWAS), genes in pathways such as vesicle-mediated transport, synaptic signalling, neuron projection development, and proteolysis were found to be shared between AD and PD. Specifically, *APOE, HLA-DRB5* and *MAPT* were GWAS candidate genes for both AD and PD. Furthermore, pathways of intracellular processes (apoptosis, autophagy, mitochondrial function, oxidative damage/repair, proteasome), local tissue environment (cell adhesion, endocytosis, neurotransmission, prions/transmissible factors), systemic environment (inflammation/immune system, lipid/metabolic/endocrine, vascular factors) as well as development and ageing (epigenetics, neurotrophic factors, telomeres) were shared between AD and PD. Genes that were similarly perturbed by PD and AD include synaptic vesicle genes (*SYT1*), Alzheimer's-related genes (*APP, SNX2*), insulin genes (*IRS4*) and oxidative stress genes (*GSTM1*) [42]. In addition, mitochondrial dysfunction genes are common between AD and PD [43]. In a study by Flores-Dorantes *et al.* (2020), some genes that are normally associated with obesity have also been report in AD and PD [44]. These include *NPY* [45, 46], *SIRT1* [47-49] and *TNFα* [50, 51] genes.

Regulatory elements such as microRNAs (miRNAs) also play an important role in AD and PD. Dysregulations of miRNAs related to axonal guidance, apoptosis and inflammation have been implicated in AD and PD. Hence, the pathways regulated by these miRNAs such as APP, L1 cell adhesion molecule (L1CAM) and caspases may represent promising therapeutic targets in AD and PD [52]. A previous study also reported epigenetic changes of genes in cell communication, apoptosis and neurogenesis were related to AD and PD [53].

There are other types of pathogenesis reported in AD and PD. Circumstantial evidence has shown that metals are involved in the development of the disease [54], for example, abnormal iron accumulation could be associated with AD and PD [31]. Besides, neuropathologic loss of locus coeruleus (LC) noradrenergic neurons has been noted in both AD and PD [55], and it has been shown to be associated with the regulation of nicotinic acetylcholine receptors [31].

Amble evidence has shown AD and PD may share some common aetiologies as well as mechanisms of pathogenesis. Hence, the treatments that are useful for AD might be similarly effective for PD, and vice versa.

COMPLEMENTARY AND ALTERNATIVE MEDICINE – THE PROMISING THERAPEUTIC APPROACH FOR ALZHEIMER'S AND PARKINSON'S DISEASE

Due to the world-wide increase of life expectancies, AD and PD have now presented a great financial burden for health care systems. The is no cure for these two diseases currently, and existing drugs are merely alleviating the symptoms of the diseases [56]. Therefore, the search for new drugs and therapeutic methods has become important. In recent decades, CAM has become very popular in the treatment of chronic diseases. The use of CAM in the prevention of neurodegenerative diseases is comparatively a newer area [57]. Natural products especially those from the traditional Chinese medicines (TCM), are the most important sources of drugs [58]. The less toxic effects, availability, and lower price of medicinal plants make them the excellent agents in the treatment of neurodegenerative diseases [59].

Natural products have been properly documented for their various biological properties such as antioxidant, anti-inflammatory and anti-apoptotic activities [60]. The anti-oxidative and anti-inflammatory natural therapeutics have shown to play a crucial role in protecting neurons [57]. Many studies have focused on the potential use of natural antioxidants to target the oxidative stress in neurological disorders over the last decade [56]. The few antioxidants that were studied for their promising neuroprotective effects include caffeine, trigonelline, shogaol, curcumin, resveratrol, baicalein, wogonin, ginsenosides, tanshinones, withanolides, picrosides, parthenolide, cannabinoids, Devil's claw, white willow bark, as well as Chinese formulations Renshen Shouwu and Shengmai San [57]. Blueberries and lingonberries that have high amounts of polyphenols (such as flavonoids) which act as potent

antioxidants could also be beneficial in treating the neurodegenerative disorders [61]. Furthermore, treatment with flavonoids such as curcumin, lycopene, ginsenoside, vitexin, and baicalin have shown promising neuroprotective effects due to their anti-amyloidogenic effect and ability to reduce the loss of dopaminergic neurons in the brain [62]. Thus, antioxidant compounds could be used in preventing or counteracting neuronal cell death and nutraceutical supplementation could be useful in the early phases of neurodegenerative diseases [63].

Besides oxidative stress, neurodegenerative diseases may be related to autophagic dysfunction. Some natural compounds such as resveratrol, curcumin, tripterine, and paeoniflorin can eliminate abnormal protein aggregates by regulating autophagy [64]. Pathogenesis of neurodegenerative may also involve dysfunctional glutamate system. Natural constituents from TCM have shown to regulate the signalling pathways of glutamate system, hence leading to protection against neurological disorders [65]. In short, various evidence have supported the promising effects of CAM on neurodegenerative diseases, including AD and PD.

NATURAL PRODUCTS

NATURAL PRODUCTS FOR ALZHEIMER'S DISEASE

Curcumin is extracted from *Curcuma longa* of the Zingiberaceae family. *C. longa* has long been used extensively to treat many illnesses in Ayurvedic medication [66, 67]. *C. longa* preparations may be administered to treat urinary tract and skin diseases, hepatic disorders, flatulence, and as a "blood purifier" [68-70]. Curcumin is a commonly consumed spice in India and was depicted to be neuroprotective against AD. This may justify the fact that India has the lowest prevalence of AD in the world, as evidenced by epidemiological studies [71, 72]. Previous studies showed that curcumin possesses neuroprotective properties such as antioxidant and metal chelation activity, as well as prevention of βA formation in AD patients [66, 67, 73]. However, further clinical investigations to verify its claims are warranted.

In vivo evidence has also proven that curcumin readily penetrates the blood-brain barrier and lowers cholesterol levels, hence potentially reducing AD risks [69, 74]. Several animal studies demonstrated that curcumin inhibited inflammation, amyloid formation, and oxidative damage in AD mice models [75-77]. Curcumin reduced levels of oxidised proteins and the inflammatory cytokine IL-1β in the brains of mice with mutant amyloid precursor protein (APPsw) expression [78]. Furthermore, there was a significant decrease in amyloid as well as plaque burden in the brains of APPsw mice fed with low-dose (160 ppm) curcumin. However, researchers failed to demonstrate that curcumin was significantly effective in a 24-week clinical trial that used 2 g or 4 g per day of Curcumin C3 Complex® in 36 mild-to-moderate AD patients [79]. This may be due to the poor bioavailability or ineffectiveness of curcumin as a therapeutic compound. Efforts to enhance the bioavailability of curcumin in the body include work by Shoba *et al.* (1998), who found that piperine could be used as an adjuvant by blocking specific metabolic pathways [80]. However, the manner how this affects the efficacy of AD treatment is yet to be evaluated.

Ginkgo biloba extracts have been long used in TCM to treat cognitive disturbances, blood circulation problems, tinnitus, and asthma. The standardised extract of *G. biloba* leaves, EGb 761, contains ginkgo-flavonol glycosides (24%) and terpene lactones (6%). The active compounds of *G. biloba* have antioxidant and anti-inflammatory properties which help protect neuronal membranes, maintain neurotransmission function, and slow cell deterioration [81]. EGb 761 promotes vasodilation, improves cerebral blood flow, reduces βA formation and inhibits platelet aggregation, as evidenced by *in vitro* and *in vivo* studies [82-88]. In addition, it improves hippocampal neurogenesis in mice [89], although there is a lack of clinical evidence to delineate the efficacy of this extract.

Numerous studies showed that *G. biloba* extracts improved cognitive function in AD patients. Kanowski and Hoerr (2003) demonstrated that 240 mg daily of EGb 761 for two weeks proved significantly more beneficial than placebo on cognition of AD patients [90]. In addition, Napryeyenko *et al.* (2009) reported positive findings in AD patients administered with 240 mg EGb 761 daily for 22 weeks, in a randomised controlled trial [91]. Another study also demonstrated that EGb 761 enhanced cognition in AD patients with mild to very mild cognitive loss [92]. Furthermore, in a 24-week clinical trial with 410 patients suffering from AD or vascular dementia, treatment with a daily dose of 240 mg EGb 761 was demonstrated to be safe and effective in cognition enhancement [93].

However, another clinical study on subjects without dementia revealed contradictory evidence. The Ginkgo Evaluation of Memory (GEM) study reported that administration of 120 mg EGb 761 twice daily for a median of 6.1 years was not effective at preventing dementia and decline of cognitive function in 3069 healthy participants aged 75 years or older [94]. The long-term use of 120 mg EGb 761 twice per day was also not effective at preventing AD in another clinical trial [95]. Similarly, a daily dose of 240 mg EGb 761 did not prevent cognitive decline in 118 subjects aged 85 years or older with no cognitive impairment [96]. Thus, it seems that *Ginkgo* improves cognition in AD patients but does not prevent the onset of AD.

Other herbal products that may act as possible agents against AD include *Centella asiatica*, *Cistanche tubulosa, Arabidopsis thaliana, Artemisia amygdalina,* and *Zizyphus jujuba* var. *spinosa. C. asiatica* has been widely used in African, Ayurvedic, and TCM in the treatment of various

diseases. In a study conducted by Chiroma *et al.* (2019), the plant showed a strong potential to prevent d-galactose/aluminum chloride-induced AD-like pathologies [97]. In China, *C. tubulosa* aqueous extract has been used as a botanical prescription drug for the treatment of dementia. The extract inhibited aggregation and deposition of Aβ [98]. In an experiment using Drosophila flies expressing human Aβ protein, the polyphenolic extract of *A. thaliana* restored the locomotor activity in these flies [99]. Sajjad *et al.* (2019) showed that *A. amygdalina* is potentially served as a therapeutic agent for AD due to its ability in inhibiting reactive oxygen species (ROS) and mitochondrial membrane potential (MMP) loss triggered by hydrogen peroxide (H_2O_2) [100]. Additionally, the ethanol extract of *Z. jujuba* seeds was found to alleviate AD-like symptoms in mice by regulating plasmin activity [101].

Extracts of *Pleurotus ostreatus* and *Laetiporus sulphureus* have been shown to effectively inhibit acetylcholinesterase (AChE) and tyrosinase in AD [102]. On the other hand, Yadav *et al.* (2019) had tested the phenolic compound rich fraction of *Trianthema portulacastrum* on a scopolamine-induced rodent model, and results showed that the fraction attenuated cognitive impairment through AChE inhibition [103]. Other extracts that may inhibit AChE include root extracts of *Heracleum verticillatum* and *Heracleum angustisectum* [104]. A recent study suggests that *Rhodiola crenulata* extract exerted its cognition protection effects by increasing acetylcholine, choline acetyl transferase and superoxide dismutase, as well as decreasing malondialdehyde levels in AD [105]. *R. crenulata* extract also regulated tryptophan, sphingolipid and glycerophospholipid metabolism in AD rats [106]. The neuroprotective effect of *Myrtus communis* was investigated using a scopolamine-induced rat model and results showed that the plant increased muscarinic (M_1 subtype) and acetylcholine receptor expression levels in their brains [107].

Karakaya *et al.* (2019) found that coumarins isolated from *Zosima absinthifolia* could serve as potential anticholinesterase compounds [108]. Lignans from *Schisandra chinensis* (Turcz.) Baill could regulate APP and neurotransmitter metabolisms as well as interrupt the formation of neurofibrillary tangles; hence improving cognitive function [109]. In addition, *Schisandra* polysaccharides may reduce phosphorylation of tau protein, deposition of Aβ and oxidative damage in AD rats [110]. Luteolin isolated from *Cirsium japonicum* var. *maackii* (Maxim.) Matsum showed strong inhibitory effect against α-glucosidase and BACE1 [111].

Recently, scientists have identified a new compound known as embelin, which inhibits AChE, butyrylcholinesterase and BACE1. The compound, derived from *Embelia ribes*, displayed potential in halting the formation of βA oligomers, improving cholinergic-transmission as well as increasing βA clearance [112]. Trans-crocin 4 and trans-crocetin, isolated from *Crocus sativus*, were found to regulate the amyloidogenic pathway and tauopathies in an AD *in vitro* model [113]. Through a systems pharmacological approach, Sun *et al*. (2019) found that various compounds derived from *Ohwia caudate*, an herb commonly used in TCM, may effectively alleviate AD symptoms through the modulation of AD-related signalling pathways and biological processes [114]. Ginseng and its active compound, ginsenoside, are also well-known for their anti-AD effects [115]. Besides that, pycnogenol extracted from the bark of *Pinus pinaster* Aiton subsp. *atlantica* is well-known for preventing mild cognitive impairment and AD [116].

NATURAL PRODUCTS FOR PARKINSON'S DISEASE

The use of plant or herbal remedies for Parkinson's disease has also been objectively evaluated in recent years. *Mucuna pruriens* (velvet beans), predominantly used in Ayurvedic treatment, is one of them. In a study on 6-hydroxydopamine (6-OHDA)-lesioned rats, it was found that *M. pruriens* extract alleviated Parkinsonism while reducing the risk of drug-induced dyskinesia more significantly than levodopa alone, or levodopa coupled with benseraside (a dopa-decarboxylase inhibitor) [117]. *M. pruriens* extract also improved the posture and motor functions of paraquat-induced PD mice [118]. It reduced oxidative stress in rat nigrostriatal tissue by reducing levels of nitrite and malondialdehyde while increasing brain catalase activity. There was also an increase in the number of dopaminergic neurons in the brain after treatment with the extract. On the other hand, when *M. pruriens* ethanolic extract was compared against oestrogen in a 1-methyl-4-ethyl-1,2,3,6-tetrahydropyridine (MPTP)-induced PD mouse model, the former ameliorated Parkinsonism in terms of balance, coordination, and motility, but not improvement in walking errors [119]. *M. pruriens* also showed strong antioxidant properties and improved the expression of tyrosine hydroxylase (TH), which drove inducible nitric oxide synthase and glial fibrillary acidic protein to normal levels, demonstrating the extract's potential in promoting neuronal injury recovery.

Using a 6-OHDA-induced cell model, the neuroprotective effects of *Bifurcaria bifurcate*, a type of seaweed that is mainly found on the Atlantic coast, were evaluated. Fractions derived from the plant showed potential in preventing MMP changes and reduced the level of H_2O_2. Furthermore, the fractions increased the viability of the neuroblastoma cell line SH-SY5Y [120]. The aqueous extract of *Davallia mariesii*, tested on B35 neuroblastoma cells induced by 6-OHDA, decreased cell apoptosis and restored mitochondrial expression *via* reduction of ROS and nitric oxide levels. It also increased the levels of glutathione and its corresponding peroxidase and reductase enzymes, while attenuating malondialdehyde levels [121].

In a study by Maiolo *et al*. (2018), SH-SY5Y cells transfected with human TH isoform 1 and treated with H_2O_2 were exposed to bioactive compounds such as cinnamaldehyde (from cinnamon), caffeoyltyramide (hemp seed extract) and piceatannol glucoside (*polygonum cuspidatum* extract) [122]. Cell viability studies showed that all the compounds exerted protection against H_2O_2-induced cell death. Another extract with a potent antioxidant effect, *Zizyphus spinachristi*, inhibited 1-methyl-4-phenylpyridinium (MPP^+)-induced damages in SH-SY5Y cells [123].

The anti-Parkinsonism effects of various natural products were also tested *in vivo* with the use of 6-OHDA- and MPTP-induced rodent models. Oral administration of *Humulus japonicas* fraction in unilateral 6-OHDA-lesioned mice had been shown to relieve motor impairment in the animals. Apigenin and luteolin which were isolated from the fraction inhibited monoamine oxidase B enzyme activity *in vitro* [124]. Furthermore, silymarin (extracted from *Silybum marianum*) may prevent cellular apoptosis in 6-OHDA-lesioned rats through the inhibition of B-cell lymphoma-2-associated X (Bax), caspase-3 and toll-like receptor 4 [125].

In another 6-OHDA-induced rat model, Xiang *et al*. (2018) showed that *Azadirachta indica* was able to suppress a myriad of enzymes and transcription factors such as catalase, glutathione peroxidase, inducible nitric oxide synthase, acetylcholinesterase, cyclooxygenase-2, Bax, cytochrome c, p53, caspase-3 and caspase-9, suggesting the potential neuroprotective role of the plant in PD [126]. Gastrodin, which is extracted from *Gastrodia elata* and *Galeola faberi*, were found to suppress 6-OHDA-induced motor impairment in rats by restoring oxidative balance in the substantia nigra pars compacta of the brain [127]. Partial recovery of behavioural changes were observed in 6-OHDA-challeged rats treated with *Aspidosperma pyrifolium* Mart extract, proven to possess strong antioxidant and anti-inflammatory activities [128].

Astragalus polysaccharides were found to be highly effective in a mouse model of PD. It attenuated MPTP-induced motor dysfunction, increased MMP and the number of TH-expressing cells, reversed mitochondrial damage and reduced ROS, cytochrome-c and caspase-3 levels in mice [129]. Similarly, the leaf aqueous extract of *Dendropanax morbiferus* has been shown to effectively curb neuroinflammation and improve behavioural deficit in MPTP-induced mice by restoring TH levels in the brain, hence rescuing the dopamine-expressing neuronal cells [130]. Another natural compound, gintonin, a ginseng-derived glycolipoprotein, may modulate α-synuclein formation, neuroinflammation and apoptosis in an MPTP-induced mouse model. Its neuroprotective effects were associated with the regulation of the nuclear factor erythroid 2-related factor 2/ heme oxygenase-1 pathway [131]. A separate study on MPTP-induced PD in C57BL/6 mice showed that *Apium graveolens* L. mediated neuroprotection *via* its antioxidant effect [132].

Several other chemically-induced *in vivo* models as well as transgenic animals were utilised in the investigation of the anti-Parkinsonism effect from traditional herbs or plants. Alzahrani *et al.* (2018) provided evidence that the *Tribulus terrestris* extract may protect the brains from rotenone-induced oxidative damage and dopamine neuronal loss in a rodent model [133]. Bao *et al.* (2018) demonstrated the beneficial effect of a Chinese herbal medicine formula consisting Dihuang (*Rehmannia glutinosa* Libosch), Roucongrong (*Cistanche deserticola* Y.C.Ma), Niuxi (*Achyranthes bidentata* Bl.) and Shanzhuyu (*Cornus officinalis* Sieb. et Zucc) on reversing the rotenone-induced death of TH-positive neurons in rats [134]. Likewise, the hydro-alcoholic extract of *Olea europaea* L. leaf also showed neuroprotective effects in rotenone-induced rats [135]. Administration of *Eplingiella fruticosa* leaf essential oil in conjunction with β-cyclodextrin (which enhances the pharmacological profile of essential oils) showed delayed onset of catalepsy, reduced rate of oral dyskinesia, restored memory impairment, prevention of anxiety, and inhibition of dopaminergic cell death in reserpine-induced mice, suggesting the potential use of this treatment in ameliorating the symptoms of PD [136].

Paraquat neurotoxicity, used to simulate PD-like damage in the brain, had been a basis of a study by Ravi *et al.* (2018) to determine the neuroprotective effects of *Cassia tora* [137]. Results revealed that extracts from the plant reduced apoptosis and inhibited lipid peroxidation. Another interesting finding revealed that coffee may be beneficial in the treatment of PD-induced mice. Two chemical constituents of coffee, eicosanoyl-5-hydroxytryptamide and caffeine, displayed synergistic effects in preserving neuronal integrity and brain function of α-synuclein transgenic mice through the maintenance of protein phosphatase 2A, a key protein that dephosphorylates α-synuclein [138]. Another prominent herb in traditional Chinese medicine, *G. biloba*, demonstrated potential in improving the locomotor activity of A53T α-synuclein transgenic mice [139].

Other non-rodent models used in PD studies include *Drosophila* (fly), chicken and *Caenorhabditis elegans* models. Supplementation of grape skin extract (obtained from red wine-production process) in daily diets promoted autophagy and maintained mitochondrial function, and hence protected against PD pathogenesis in a *Drosophila melanogaster* model [140]. Besides, dietary supplementation of Omija, commonly known as the five-flavour berry, may enhance associative taste memory in DJ-1β mutant PD fruit flies [141]. Moreover, genistein, a compound found in *Genista tinctoria*, delayed the loss of climbing ability and increased dopamine content in PD flies [142].

On the other hand, Martins *et al.* (2018) showed that *Anacardium microcarpum* extracts exhibited neuroprotective effect *via* the activation of protein kinase B and extracellular signal-regulated kinase in 6-OHDA-induced chicken brain slices [143]. The *C. elegans* NL5901 strain which expresses human α-synuclein in muscle tissue was used as a model to assess the anti-Parkinsonian activity of *Holothuria scabra* extracts. The findings suggested reduced α-synuclein aggregation, indicating its potential use as a therapeutic agent for PD [144].

NUTRITIONAL SUPPLEMENT

NUTRITIONAL SUPPLEMENTS FOR ALZHEIMER'S DISEASE

Acetyl L-carnitine (ALCAR) is involved in lipid metabolism and energy production, and actively penetrates the blood-brain barrier as a partial direct cholinergic agonist [145]. Due to the involvement of the dysfunctional cholinergic function in AD, it is suggested that ALCAR may reduce AD pathogenesis by ameliorating βA-mediated oxidative stress. Several proposed benefits of ALCAR in terms of alleviating AD symptoms are summarised in Table 1.

Table 1. Intracellular targets of acetyl-L-carnitine (ALCAR) and its pharmacological effects

Target	Relevance to Alzheimer's disease (AD)	Pharmacological effect	References
Mitochondria	Accumulation of beta-amyloid (Aβ) in synaptic mitochondria leading to increased oxidative stress and affecting maintenance of synaptic plasticity	Improvement of synaptic plasticity	[146-148]
	Impairment of respiratory chain function in mitochondria may be induced by Aβ	Stimulation of energy metabolism	[146, 148, 149]
Protein kinase C (PKC)	PKC stimulates formation of the amyloid precursor protein (secretory form)	Amelioration of cognitive function	[150, 151]
N-methyl-D-aspartate (NMDA) receptors	Over-activated NMDA receptors in neuronal cells lead to excessive cell death in AD	Amelioration of cognitive function	[14, 15, 152]
Nerve growth factor (NGF)	NGF deficiency inducing neurodegeneration	Amelioration of cognitive function	[153, 154]
Heme oxygenase-1/biliverdin reductase (HO-1/BVR-A) system; Heat shock protein (HSP) 70	In AD, the HO-1/BVR-A system is upregulated in cells in response to increased oxidative stress. HSP regulates protein misfolding in AD	Enhancement of the cell stress response	[155-158]

ALCAR shifts APP metabolism towards the non-amyloidogenic pathway by inducing ADAM10 (a disintegrin and metalloproteinase 10) trafficking towards the postsynaptic membrane in neurons [159]. ALCAR led to reduced AD-like protein phosphatase inhibition and tau hyperphosphorylation of the rats [160]. Another piece of *in vivo* evidence showed that ALCAR significantly restored the function of acetylcholine esterase in an AD rat model [161]. The supplement exerted its beneficial effect by delaying the deterioration in cognitive function of AD patients. In a 12-week clinical trial in early-stage AD patients, the therapeutic effect of ALCAR administered at 2250-3000 mg per day was 2.8 times higher than in placebo-treated patients [162]. A meta-analysis of 21 clinical studies also showed that ALCAR either reduced cognitive deficits, or slowed cognitive deterioration [163].

Coenzyme Q10 (CoQ10) occurs naturally in the body and is crucial for the production of mitochondrial energy [164-166]. Strong emerging evidence shows that mitochondrial dysfunction leads to the buildup of oxidative stress, which is the main contributor to AD pathogenesis [167-172]. Several findings demonstrated that CoQ10 levels decline with age, suggesting a potential therapeutic role for CoQ10 in age-related neurodegenerative diseases, including AD [166, 173, 174].

Mitochondrial oxidative stress (mitochondrial superoxide) may be reduced in neurons lacking CoQ10, following 2.5 μM of CoQ10 supplementation for 5 days [175]. Treatment with CoQ10 not only reduced oxidative stress but decreased βA deposition and enhanced cognitive function in AD mice [176-178]. CoQ10 has been proven safe for human subjects and was previously used in clinical trials with Huntington's disease, but has yet to be tested in AD subjects [175]. As mitochondrial dysfunction and increased oxidative stress are implicated in the pathology of AD, the neuroprotective effects of antioxidant CoQ10 may show promising results for therapeutic trials.

NUTRITIONAL SUPPLEMENTS FOR PARKINSON'S DISEASE

Due to the anti-oxidative nature of CoQ10, it only seemed logical to be considered for PD treatment. However, a randomised clinical trial in 2014 using high dosages of

coenzyme Q10 showed that there was no correlation between the administration of the substance and clinical benefits in early PD [179]. In the study, 600 participants were grouped and assigned to take either 1200 or 2400 mg/d of coenzyme Q10 or 1200 IU/d of vitamin E (placebo). The study was terminated due to futility as the disease was progressively worsening in subjects of all three groups, finally resulting in the subjects reverting to conventional treatment.

Recently, a study was conducted to assess the efficacy of an electron-rich form of coenzyme Q10, ubiquinol-10, in PD patients [180]. Two groups of patients were recruited: group A where the patients were experiencing wearing-off (a complication that occurred after a few years of using levodopa) and group B which had not been administered levodopa. Both groups were assigned to either ubiquinol-10 or a placebo. Results showed that the patients treated with ubiquinol-10 in group A showed significant improvement in symptoms. Ubiquinol-10 was also shown to be safe and tolerable at 300 mg/day. Despite this finding, more clinical evidence is necessary to verify the benefit of ubiquinol-10 on PD patients.

ACUPUNCTURE

ACUPUNCTURE FOR ALZHEIMER'S DISEASE

Acupuncture has been an integral part of TCM; its use spanning thousands of years. It works on the theory that diseases arose from the imbalance of "Qi" flow in the body, and insertion of needles along the various pathways of energy can restore the balance. In acupuncture, practitioners insert very fine needles into the skin at a certain 'meridian points' to improve regulatory functions by stimulating nerves around the body [181]. On this basis, acupuncture remains a promising TCM therapy to treat neurological disorders [182, 183].

Several resting-state functional magnetic resonance imaging (fMRI) studies suggested that acupuncture may activate areas associated with cognition, thereby achieving its therapeutic effect on AD [184]. In a clinical trial, Wang *et al.* (2012) used fMRI to demonstrate the effects of acupuncture in his subjects, with encouraging results - improved hippocampal connectivity during the resting stage following acupuncture at acupoints 'Tai chong' and 'He gu' [185]. This suggests that acupuncture may stimulate hippocampal activity in AD patients.

ACUPUNCTURE FOR PARKINSON'S DISEASE

Similar to AD, a wave of animal model and clinical studies evaluated the positive effects of acupuncture on PD. In recent years, a novel acupuncture method known as 'bee venom' acupuncture emerged, which involved the insertion of needles coated with diluted bee venom. The findings showed that this controversial technique offered neuroprotective effects on dopaminergic neurons [186]. Results of a clinical trial suggested that both conventional and bee venom acupuncture triggered improvements on mobility, as well as in non-motor measures such as Beck Depression Inventory in PD patients [187]. After 8 weeks of either treatment, the patients showed amelioration in motor symptoms such as tremor at rest, rigidity, hand movement and postural stability, as well as the 30-minute walking time when compared to the control group. However, there was no significant difference between the effects of conventional and bee venom acupuncture groups.

A mechanistic study revealed that bee venom demonstrated neuroprotective effects by suppressing microglial activation, which releases ROS and causes dopamine neuronal damage, as well as reducing CD4 T cells into the substantia nigra of MPTP-induced mouse models [186]. Another mouse study found that apamin, a constituent of bee venom, may partially reproduce the neuroprotective effects [188]. Though both bee venom and apamin are protective against neuronal MPTP intoxication, apamin did not preserve dopamine nerve terminals. This suggests that other compounds within bee venom would possibly enhance its neuroprotective abilities.

A combined therapy regimen involving levodopa and acupuncture was also done on 6-OHDA-lesioned mice [189]. It was found that levodopa demonstrated its benefits at lower doses when combined with acupuncture, as compared to levodopa alone. When acupuncture was combined with high-dosage levodopa, the risk of levodopa-induced dyskinesia was reduced while reaping its full effect. By stimulating the acupuncture point GB34 (Yanglingquan), it was found that the prefrontal cortex and precentral gyrus was activated in PD patients but not in healthy people [190].

EXERCISE AND LIFESTYLE PRACTICES

EXERCISE AND LIFESTYLE PRACTICES FOR ALZHEIMER'S DISEASE

Meditation is defined as an intentional, self-regulated, mind-body practice focused on maintaining one's attention. It is used as a means to relax or reduce stress and improve both mental and physical well-being. Meditation techniques can be classified into different categories according to its area of interests, such as mindfulness, transcendental meditation, Vihangam yoga and Kirtan Kriya [191].

Although the pathogenesis of AD remains uncertain, studies suggested the common conditions associated with cognitive impairment including chronic stress, poor sleeping quality and mood disturbance have been correlated to the development of memory loss in AD [192-194]. Literature suggests that the use of meditation as a therapeutic intervention for adults works through targeting the risk factors and possibly preventing cognitive decline [195-197]. Brief meditative practices (5 days to 8 weeks)

may reduce perceived stress, depressive symptoms, sleep disturbance and improve several domains of cognition [198]. Long term meditation also have been shown to increase gray matter volume involved in attentional performance, sensory processing and interoception [199, 200]. A small clinical trial indicated that meditation exerted therapeutic effects in adults with memory disorders by reducing stress and depression, enhanced cognition and stimulated beneficial changes in brain structure and function [201].

Four potential mechanisms underlying the beneficial effects of meditation have been proposed [202-205]. Firstly, it is possibly mediated by reduced reactivity of the sympathoadrenal system and hypothalamic pituitary adrenal (HPA) axis as meditation reduces stress levels, depressive symptoms and sleep disturbances. Secondly, meditation may activate vagal stimulation thus enhancing parasympathetic function and cognition, hence decreasing the risk of cognitive decline in AD [206]. Thirdly, meditation may improve cognitive performance through the stimulation of brain structures and neurochemical systems [207]. It is also suggested that meditation may increase telomerase activity and cushion stress-induced cellular aging effects, thus reducing neuronal loss or degenerative changes which can lead to cognitive decline [208, 209].

EXERCISE AND LIFESTYLE PRACTICES FOR PARKINSON'S DISEASE

Tai Chi is described as a traditional form of martial art combining sequences of deep breathing and relaxation coupled with slow movements that maintains a variety of postures. Three randomised controlled trials have been performed for PD patients [210-212]. The largest trial conducted in 2012 recruited 195 PD patients which were divided into three groups of therapies - Tai Chi, resistance training, and stretching exercises [212]. Results showed that while all three groups had improved motor functions, the Tai Chi group had a more significant impact on postural stability and patients also had fewer falls during the observation period. Another trial that compared Tai Chi therapy with the 'no intervention' group also showed similar results [211].

The impact of Tai Chi was also compared against combined stretching-strengthening exercise on the functional fitness and life quality of people with PD [210]. Three groups were formed in the trial, namely Tai Chi, combined exercise, and control groups. Findings revealed that the Tai Chi and combined exercise groups showed improvements in physical function, whereby the combined exercise group showed improvement in the flexibility of the upper extremities while Tai Chi increased flexibility in the lower limbs as well as quickness. Amelioration of quality of life was also noted, with combined exercise excelling in the social domain whereas Tai Chi supported emotional well-being. Despite the mentioned benefits of Tai Chi, martial art did not help with gait initiation and performance. This suggests that clinicians should exercise caution before recommending Tai Chi as a therapy for PD.

Aside from martial arts, another stimulating physical activity is dance, which integrates elements such as social engagement and movement to the beat of the music. In a fascinating study, Argentine Tango was found to show potential benefits in functional mobility, care satisfaction and balance in PD patients [213]. After 12 weeks of classes, the Tango group recorded significant improvement in dynamic balance and balance during gait, as well as pivot walking. A similar study featuring community-based Argentine Tango classes showed that the sessions increased activity participation amongst PD patients over a period of 12 months [214]. Remarkably, the Tango group recovered a significant portion of physical activity that was lost with the onset of PD.

Apart from Tango, Irish set dancing was also found to be a safe and practical method for the management of PD, whereby a phase II feasibility study concluded improved mobility and better quality of life [215]. However, a larger randomised control trial is now required to determine its effectiveness in the long term. Latin American and ballroom dancing have also recorded noticeable benefits in PD patients, mainly in balance, balance confidence, and spinal posture [216]. The participants thoroughly enjoyed the activity, which prompted improvements in their well-being. However, more research is necessary to identify and evaluate the benefits of dance to PD patients.

COMPLEMENTARY AND ALTERNATIVE MEDICINE USED IN BOTH ALZHEIMER'S AND PARKINSON'S DISEASE

In the past studies, many natural products have been proven to be beneficial towards AD and PD. Tea and coffee that have been consumed for decades have shown protective effects to AD and PD in recent studies. Green tea, a nonfermented tea, is rich in polyphenols content. Recent reports demonstrate that green tea may exert a positive effect on the reduction of medical chronic conditions such as AD and PD [217]. Tea polyphenols lower the morbidity of PD and AD by reducing oxidative stress as well as regulating signalling pathways and metal chelation [218]. Furthermore, a number of studies have demonstrated the benefits of green tea catechins (such as epigallocatechin gallate) in AD and PD [219]. Tea also contains other bioactive components such as theanine, caffeine, and theaflavins. Theanine exhibits neuroprotective effects by inhibiting glutamate receptors as well as regulating extracellular concentration of glutamine while caffeine is antagonising the adenosine receptor. Theaflavins are known to possess antioxidant properties [218]. Several studies have revealed coffee consumption is inversely correlated with AD and PD. This finding may be attributed to the rich phytochemistry of coffee, such as caffeine, chlorogenic

acid, caffeic acid, and hydroxyhydroquinone. Coffee can ameliorate oxidative stress via nuclear erythroid 2-related factor 2- antioxidant response element (Nrf2-ARE) pathway. Furthermore, caffeine and its metabolites can help in improving cognitive functions [220]. Besides, caffeine can protect neurons against dysfunction and death, as evidenced in the animal models of AD and PD [221].

A number of Chinese or Indian herbal medicines have been used to treat or prevent neurological diseases such as AD and PD. These include ginseng [222], *Ganoderma lucidum* [223], *Withania somnifera* (L.) Dunal [224], and *Pueraria lobata* (Willd.) Ohwi (puerarin is the major bioactive ingredient) [225]. Wang *et al.* (2021) have reported that the beneficial effects of TCM might be related to the autophagy-related mechanisms [226]. Recent evidence indicates that polyphenols (such as resveratrol and curcumin), flavonoids (such as quercetin), polyamine (such as spermidine), and sugars (such as trehalose) have a common mechanism of action that leads to restoration of efficient autophagy [227]. In addition, Rahman *et al.* (2020) revealed that a wide variety of natural compounds such as alkaloids, terpenoids, xanthonoids, lignans, disaccharides, glycolipoproteins, and saponins are involved in the modulation of the autophagy signalling pathway [228].

Other natural products that may provide therapeutic advantages for AD and PD include mangosteen (*Garcinia mangostana* L.) pericarp and its xanthones [229], *Crocus sativus* L. [230], and echinacoside which is isolated from *Echinacea angustifolia* DC. [231]. Besides, mangiferin (MGF, 2-C-β-D-glucopyranosyl-1, 3, 6, 7-tetrahydroxyxanthone), which is isolated from *Mangifera indica* L. has shown to possess multipotent properties starting from antioxidant effects to the alleviation of mitochondrial dysfunction, neuroinflammation, and cellular apoptosis. It can cross the blood-brain barrier to exert neuronal protection, hence is able to improve the declined memory and cognition [232]. *Uncaria rhynchophylla* (Miq.) Jacks is a common herbal medicine known as Gou-teng in Chinese. *U. rhynchophylla* and its major components such as rhynchophylline and isorhynchophylline have been shown to have neuroprotective effects on AD and PD through antioxidative, anti-inflammatory and neurotransmitters regulatory mechanisms [233]. On the other hand, silymarin is the major constituent of milk thistle extract. It is most commonly known for hepatoprotective effect but has been reported on other therapeutic effects such as anti-Alzheimer and anti-Parkinson recently [234]. *Nigella sativa* L. that has been utilised as a medicinal plant due to its anti-tumour, anti-microbial, anti-histaminic, immunomodulatory, anti-inflammatory, and anti-oxidant effects, is also used for AD and PD recently. Thymoquinone is the main active components of the volatile oil of *N. sativa* seeds [59]. A fruit known as açaí (*Euterpe oleracea* Mart.) has been proposed as the potential therapeutic agents for diseases such as PD and AD because it has significant amount of anthocyanins, which contributing to the antioxidant property [235].

Many therapeutic compounds are derived from natural products. As such, several natural ergot alkaloids were discovered and unnatural analogs were synthesised to treat an array of diseases, including AD and PD [236]. Plant iridoids, for example catalpol and its 10-O-trans-p-coumaroyl derivative, have been found to slow down the process of neurogedeneration in AD and PD by increasing the expression of insulin degrading enzyme, neprilysin, peroxisome proliferator-activated receptor-γ, and α-secretase, as well as decreasing the expression of BACE1 to reduce the levels of βA oligomers. These plant metabolites also reduced the tau protein hyperphosphorylation and neurofibrillary tangles formation. Neuroprotective proteins such as B-cell lymphoma-2, growth-related protein-1 receptor, protein kinase C, and mitogen-activated protein kinase kinase were activated by these iridoids, while the expressions of pro-apoptotic proteins, Bax and caspase-3 were suppressed. Furthermore, these plant metabolites improved the lysosomal autophagy process. More importantly, these plant metabolites reduced the cognitive impairment by increasing the expression of synaptic proteins [237].

Lipid nutrient is an example of nutraceutical approach in managing AD and PD. Lipids, whether in the form of vegetable or animal oils or in the form of fatty acids, could be incorporated into diets with the aim of preventing the AD or PD. These different lipids can prevent cell death in the neurodegenerative diseases. In the future, these lipids can be delivered better to the brain by utilising lipid encapsulation [238]. Clinical trials and population studies indicate that the Mediterranean diet and its main lipid component, extra-virgin olive oil which contain many phenolics, are effective against AD and PD *via* interference with the aggregation of peptides or proteins found in amyloid diseases [239].

CONCLUSION

The conventional treatments developed for AD and PD so far are only aimed at symptomatic treatment and are not known to be curative. Thus, a major breakthrough in treatment alternatives would be necessary and timely. CAM represents a feasible repertoire of alternative therapies as it has shown promising results in neurodegenerative disease management. This should warrant future exploration to develop better therapeutic choices.

The data on CAM efficacy, although spanning a wide scope, is generally exploratory and its clinical effects are largely unverified. Thus, clinical studies at a larger scale should be performed to systematically validate its effects. Inconsistencies have been observed in the experimental evidences and clinical data due to the variability in doses, methodological challenges, and population demographics. There are still gaps of knowledge regarding when to initiate

the treatment, how to treat, duration of the treatment, and the potential side effects. Therefore, more well-designed randomised controlled trials, with clear and precise indications for appropriate doses of CAM at various stages of the diseases are essential. In addition, research on the synergistic use of CAM along with conventional treatments are worth exploring in the endeavor to discover an effective management regimen for neurodegenerative diseases.

ACKNOWLEDGMENT

This review was supported in part by the Ministry of Higher Education, Malaysia [grant no. FRGS/2/2014/SKK01/MUSM/03/1].

CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest regarding the publication of this manuscript.

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