Original Article

Effects of plant-derived dietary antioxidants on Alzheimer's disease: Focus on ferroptosis

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Background and Objectives: Alzheimer's disease (AD) is the most prevalent form of dementia in older individuals. Ferroptosis, a programmed cell death characterized by iron-dependent membrane lipid peroxidation is implicated in AD pathology. Increasing evidences have shown that plant-derived dietary antioxidants exhibit their anti-ferroptosis activity. However, the anti-AD mechanism of plant-derived dietary antioxidants remains elusive. Therefore, this review aims to explore the anti-AD effects of plant-derived dietary antioxidants via ferroptosis regulation. **Methods and Study Design:** This review examines the available published data from all peer-reviewed original research articles on following topics: ferroptosis mechanisms, the role of ferroptosis in AD, the preclinical or clinical studies of plant-derived dietary antioxidants in cell, animal models of AD or patients with AD. **Results:** Ferroptosis is involved in AD pathology. Importantly, we clarify why docosahexaenoic acid (DHA)-rich brain phospholipids are extremely susceptible to lipid peroxidation. In addition, plant-derived dietary antioxidants such as vitamin E (VE), resveratrol, epigallocatechin-3-gallate (EGCG), curcumin, quercetin, baicalein and alpha-lipoic acid (ALA) show the anti-AD effects in preclinical AD models and prevent decline of cognition in healthy elderly population. Clinical studies show that ALA prevents decline of cognition of AD patients although most plant-derived dietary antioxidants exhibit conflicting results. **Conclusions:** It suggests that a plant-based diet may lead to potential health benefits in preventing cognitive decline in healthy elderly population. In regard to ALA, further clinical studies are highly recommended to evaluate its therapeutic potential that could optimize its dietary intake for preventing and alleviating decline of cognition of patients with AD.

Key Words: Alzheimer's disease, ferroptosis, β-amyloid peptide, tau protein, plant-derived dietary antioxidants

INTRODUCTION

Alzheimer's disease (AD) is a most common insidious and chronic neurodegenerative brain disease and the leading prevalent cause of dementia in the elderly, accounting for approximately 70% of all dementia cases globally. The World Health Organization (WHO) notes that the number of people living with dementia globally is expected to rise from 55 million in 2019 to 139 million in 2050. The economic costs of dementia are also expected to more than double from US$1.3 trillion per year in 2019 to $2.8 trillion dollars by 2030.[1, 2] In most cases, AD is characterized by progressive memory impairment and cognitive decline, affecting behavior, speech, visual-spatial orientation, and fine motor system. Pathologically, AD is mainly characterized by brain atrophy, extracellular senile plaques composed primarily of abnormally folded amyloid-β (Aβ) peptide, intraneuronal neurofibrillary tangles made up of hyper-phosphorylated microtubule-associated protein tau, and loss of neurons and synapses.[3-5] Other factors are also implicated in exacerbating neurodegeneration processes such as altered metal homeostasis, neuroinflammation, oxidative stress, lesions of cholinergic neurons.[6, 7] Generally, a complex combination of behavioral, genetic, and environmental risk factors is proposed as etiologies of AD,[8-10] the real cause of AD, however, still a controversy, but ageing is the leading risk factor for its onset.[11]

AD is a slowly progressive and irreversible brain disorder. Previous therapeutic strategies have focused mainly on reducing the levels of Aβ and hyperphosphorylated tau, the two key components of the amyloid cascade.[12] Small-molecule drugs such as β-secretase converting enzyme inhibitors or anti-amyloid-β monoclonal antibodies have been designed to inhibit Aβ production or aggregation, enhance Aβ clearance or neutralize neurotoxic Aβ oligomers/plaques.[13, 14] Tau aggregation inhibitors or antibodies were specifically designed to block larger intracellular tau aggregation and toxicity.[15-17] Unfortunately, to date, none of these drugs have been shown to slow the progression of AD with the cost of several billion dollars and decades of research, shedding mounting doubt on the validity of amyloid cascade hypothesis, the long postulated pathological model of AD.[18, 19] Given a series of failed

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clinical trials focusing on lowering pathological amyloid and tau, new targets or aspects of neurodegeneration in AD are of great interest and urgently need to be explored to find potential disease-modifying therapeutic strategies[20, 21] Of particular interest is the potential role of ferroptosis in the pathogenesis of AD, a recently identified mode of nonapoptotic regulated cell death driven by iron dependent accumulation of lipid hydroperoxides.[22-24] In recent years, mounting evidence suggests that ferroptosis has been implicated in AD progression and targeting ferroptosis might provide new therapeutic opportunities in treating AD.[25-28] The term ferroptosis was coined by Dixon et al. in 2012, although the toxicity of iron and lipid peroxidation was reported half century ago. Ferroptosis is morphologically, biochemically and genetically distinct from apoptosis, autophagy, pyroptosis and other types of regulated cell death.[22] Cells undergoing ferroptosis usually exhibit necrosis-like morphological changes including a loss of plasma membrane integrity, rupture of cell outer-membranes, swelling of cytoplasmic organelles accompanied by shrunken mitochondria, reduced or absent mitochondrial crista and outer mitochondrial membrane rupture without apoptosis features such as chromatin condensation and apoptotic body formation.[29-31] Although the exact mechanism of ferroptosis is not well understood, it is of note that ferroptosis is tightly linked to iron dyshomeostasis, peroxidation of membrane long chain polyunsaturated fatty acids (PUFA) and loss of antioxidant defense.[24, 32, 33]

Growing evidence has shown that certain dietary compounds, especially antioxidants play a beneficial role in brain aging and neurodegenerative disease. In this review, on one hand, we summarize the molecular mechanism of ferroptosis and its role in AD pathology. In another hand, we summarize the neuroprotective activities of VE, resveratrol, EGCG, curcumin, quercetin, baicalein and ALA. We delve into the efficacy of these natural antioxidants to counteract neuronal dysfunctions underlying AD pathogenesis.

METHODS

Regarding mediation analysis, the current approach used by the authors could not get the accurate estimates of direct and indirect effects. If the authors do not plan to conduct additional analyses following proper mediation analysis procedures, they should avoid using terms such as "two-step approach" or drawing conclusions related to mediation effects in the manuscripts.

RESULTS

Regulatory mechanisms of ferroptosis

Iron metabolism in ferroptosis

Different from apoptosis, necrosis, autophagy and other modes of regulated cell death, ferroptotic cell death is strictly dependent on iron availability.[34]

Iron usually exists in oxidized ferric status (Fe^{3+}) and reduced ferrous status (Fe^{2+}), respectively. Extracellular $Fe3^{+}$ binds to transferrin, an extracellular glycoprotein and was recognized and delivered into the cells by transferrin receptor (TFRC), a type II transmembrane glycoprotein (Figure 1).[35] After absorption by TFRC, Fe3+ is reduced to Fe2+ by six-transmembrane epithelial antigen of prostate 3 (STEAP3), a metalloreductase in the endosome, and then released into cytosol through divalent metal transporter 1 (DMT1), a mammalian transmembrane proton-coupled metal-ion transporter.[36, 37] Cellular labile iron pool (LIP) is predominantly composed of ferrous iron and maintained within a relative stable status (iron homeostasis) through orchestrated regulation of iron uptake, utilization, storage and export.[38, 39] For example, excessive build-up of LIP can be regulated by transport out of the cell by ferroportin, the only known cellular iron exporter or stored mostly as inert iron in ferritin cages. whereas autophagic degradation of ferritin (ferritinophagy) by nuclear receptor coactivator 4 (NCOA4) releases iron stored in ferritin into LIP.[40] In addition, haeme-oxygenase 1 (HO-1)-mediated haeme degradation also contributes to LIP contents.[41, 42]

Abnormal intracellular iron distribution or iron overload in cells can trigger lipid peroxidation either enzymatically or nonenzymatically via the Fenton reaction (Figure 1). Excess iron initiates Fenton reaction by catalyzing PLOOHs, an essential free radical precursor to generate the alkoxyl phospholipid radical PLO• and the phospholipid peroxyl radical PLOO•, and driving the damaging peroxidation chain reaction.[43, 44] In iron-dependent enzymatic lipid peroxidation, iron acts as an essential cofactor for enzymes that directly catalyze the peroxidation of lipids (such as iron-containing dioxygenase, lipoxygenase and oxidoreductase).[45]

Lipid peroxidation drives ferroptosis

It is well known that acyl-coenzyme A (CoA) synthetase long chain family member 4 (ACSL4) and lysophosphatidylcholine acyltransferase 3 (LPCAT3) are two key membrane-remodelling enzymes mediating the synthesis of PUFA-(phospholipids) PLs.[46] ACSL4 catalyses the ligation of coenzyme A (CoA) groups with free PUFAs, such as arachidonic, adrenic and linoleic acids to generate PUFA-CoAs.[47] These modified PUFAs can be re-esterified and integrated into membrane PLs by LPCAT3 to form PUFA-PLs. Acetyl-CoA carboxylase (ACC) is a biotin-dependent enzyme and catalyzes the carboxylation of acetyl-CoA to form malonyl-CoA, which is an intermediate in the de novo synthesis of long-chain fatty acids and plays a pivotal role in fatty acid metabolism.[48, 49]

Lipid peroxidation process is shown in Figure 1. Membrane PUFA-PLs are highly susceptible to lipid peroxidation because of their reactive bis-allylic hydrogens. [50] They may undergo lipid peroxidation via non-enzymatic autoxidation driven by iron-mediated Fenton reaction and iron-containing lipoxygenases, particularly 12/15 lipoxygenases or oxidoreductase cytochrome P450,[51, 52] although conflicting results about the role of lipoxygenases in ferroptosis were reported.[53] Lipid peroxidation generally consists of three phases: initiation, propagation and termination.[54] In the initiation phase, reactive oxygen species including the hydroxyl (OH•) radicals converting from H_2O_2 via Fenton reaction, reactive nitrogen species and reactive lipid species remove a bisallylic hydrogen atom from the membrane PUFA to form a phospholipid radical (PL•).[55, 56] In the propagation phase, the formed phospholipid radical (PL•) rapidly reacts with molecular oxygen to form PLOO•. PLOO• then reacts with another

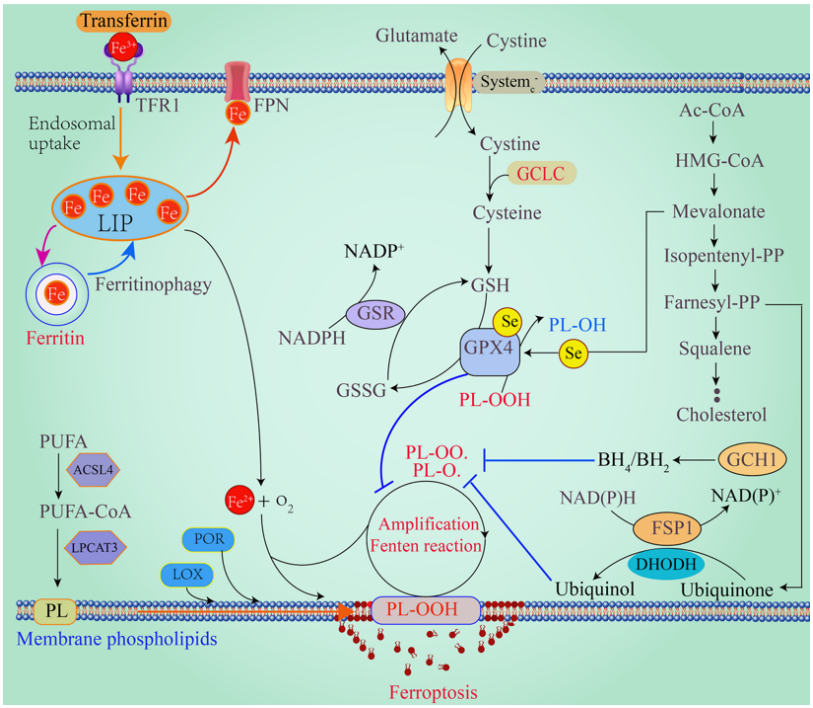

Figure 1. Molecular mechanism of ferroptosis. The transferrin receptor (TFRC) facilitates the entry of Fe^{3+} into the cell, which is reduced to Fe^{2+} by metalloreductase (STEAP3) in the endosome and transported into the labile iron pool (LIP). Excess iron from LIP is stored in ferritin which can be degraded by ferritinophagy. In addition, ferroportin (FPN) facilitates Fe^{2+} export. Free PUFA are activated by acyl-coenzyme A (CoA) synthetase long chain family member 4 (ACSL4) and lysophosphatidylcholine acyltransferase 3 (LPCAT3) to generate membrane phospholipids (PL). PL undergoes lipid peroxidation and forms phospholipid hydroperoxides (PLOOH) via non-enzymatic (Fenton reaction) and enzymatic (lipoxygenases (LOX) and/or cytochrome P450 oxidoreductase (POR)) processes. PLOOH can react with cellular labile Fe^{2+} to generate alkoxyl and peroxyl radicals, which can react with other PUFA and results in the propagation of PLOOH production. The classical ferroptosis-inhibiting axis includes uptake of cystine via the system xc - cystine–glutamate antiporter, which is crucial for glutathione (GSH) synthesis. Glutathione peroxidase 4 (GPX4) coverts PLOOH to PL-OH by the use of reduced GSH as a substrate and protects cells from oxidative stress. Oxidized glutathione (GSSG) is reduced to GSH via glutathione–disulfide reductase (GSR) using electrons provided by NADPH. Other ferroptosis suppressive mechanisms include farnesyl-diphosphate farnesyltransferase 1 (GCH1)/ di/tetrahydrobiopterin (BH2/BH4) pathway, the ferroptosis suppressor protein 1 (FSP1)–ubiquinone system and mevalonate pathway, which mediate inhibition of lipid peroxidation and protect cells from ferroptosis induction. Ac-CoA, Acetyl-CoA; HMG-CoA, 3-hydroxy-3-methylglutaryl CoA

PUFA to generate phospholipid peroxide (PLOOH) and a new PL•.[57] Of note, lipoxygenases or oxidoreductase has been implicated in catalyzing PL to form PLOOH. If the toxic PLOOH is not reduce to a nontoxic phospholipid alcohols (PLOH) by glutathione peroxidase 4 (GPX4), PLOOH and free radicals, especially lipid free radicals such as PLOO• and PLO• will react with PUFA-PLs to produce more PLOOHs.[58, 59] This chain reaction may trigger the breakdown of membrane integrity, membrane permeabilization, and ultimately rupture of organelle and/or cell membranes.[60, 61] This termination step will occur by lack of lipid substrates or endogenous antioxidant enzymes such as GPX4 or antioxidants such as VE.

Unlike PUFA, ACSL3-dependent activated phospholipid-monounsaturated fatty acids (MUFA-PL) such as oleic acid-phosphatidylethanolamine and palmitoleic acid-phosphatidylethanolamine have been demonstrated to suppress lipid peroxidation and ferroptosis by displacing PUFA from PLs in cellular membranes.[62-64]

Collectively, the type and abundance of long chain fatty acids (LCFAs) in membrane PLs are two determinants of ferroptosis vulnerability of cells, highlighting the complexity of ferroptosis induction at the cellular levels.

The system Xc-/GSH/GPX4 axis: the primary defense system against ferroptosis

GPX4, a selenoprotein, belongs to the GPX protein family and is the primary anti-ferroptosis enzyme capable of reducing potentially toxic PLOOHs to non-toxic PLOH using two molecules of glutathione (GSH) (Figure 1).[65] Reduced GSH is a thiol-containing tripeptide consisting of glycine, glutamate and cysteine, with cysteine being the rate-limiting for the biosynthesis of GSH. Extracellular cystine (an oxidized dimeric form of cysteine) is transferred into cytosol via cystine-glutamate antiporter, known as system Xc- and reduced to cysteine. System Xc- is a heterodimeric protein complex composed of the 4F2 cell-surface antigen heavy chain (4F2hc or SLC3A2) and amino acid-transporter solute carrier family 7 member 11 (SLC7A11 or xCT).[66, 67]

Cystine depletion via deprivation of cystine from culture media or pharmacologically inhibiting xCT with erastin or other ferroptosis inducers (FINs) will lead to GSH depletion and indirectly inactivate GPX4, ultimately inducing ferroptotic death.[68, 69] In addition, GPX4 can be directly inactivated using Ras-selective-lethal-3 (RSL3), which covalently modifies GPX4 active site selenocysteine.[70, 71] Therefore, the system Xc-/GSH/GPX4 axis is considered the main cellular defence pathway against ferroptosis.[72]

GPX4-independent ferroptosis-defence systems

It is initially believed that GPX4 was the only ferroptosis gatekeeper until ferroptosis suppressor protein 1 (FSP1; also known as AIFM2) is found to defend against ferroptosis independent of GPX4.[73, 74] FSP1 localizes on the plasma membrane where it functions as an NAD(P)H-dependent oxidoreductase that reduces ubiquinone (CoQ10) (or its partially oxidized product semihydroquinone) to ubiquinol (CoQH2) (Figure 1). Ubiquinol can trap lipid peroxyl radicals to terminate lipid autoxidation, thereby suppressing lipid peroxidation and ferroptosis. Recent studies identified that GTP cyclohydrolase 1 (GCH1) is another ferroptosis regulator via its metabolic products tetrahydrobiopterin (BH4/THB) (Figure 1).[75] It is proposed that GCH1 protects phospholipids containing two PUFA tails against oxidative degradation by generating as a direct radical-trapping antioxidant as well as being involved in ubiquinone biosynthesis.[75, 76] Dihydroorotate dehydrogenase (DHODH)–CoQH2 system is a recently revealed defence against ferroptosis that acts in parallel to mitochondrial GPX4 (but independently of cytosolic GPX4 or FSP1) to inhibit ferroptosis in the mitochondrial inner membrane by reducing ubiquinone to ubiquinol to detoxify mitochondrial lipid peroxides.[77] In addition, mevalonate pathway including isopentenyl pyrophosphate (IPP), farnesyl pyrophosphate (FPP), squalene, CoQ10, and cholesterol is involved in regulating ferroptosis (Figure 1). GPX4 synthesis requires a unique selenocysteine tRNA (Sec-tRNA). IPP, the precursor of squalene and CoQ10 is a limiting substrate for enzymatic isopentenylation of Sec-tRNA and essential for GPX4 synthesis.[78-80]

The emerging role of ferroptosis in AD

AD is a multifactorial neurodegenerative disease and has complex etiopathogenesis. Existing evidence suggests that ferroptosis is involved in AD. Iron dyshomeostasis, enhanced lipid peroxidation, and decreased GSH/GPX4 activity in AD are described below.

Iron dyshomeostasis in AD

Elevated iron was first shown in the brains of AD patients in 1953.[81] Since then, increasing subsequent studies confirmed the association between iron accumulation and the development of AD.[82, 83] Iron elevation in the brain with ageing was accompanied by cognitive decline prior to disease.[84] It was also found that cortical iron is strongly associated with the rate of cognitive decline of AD patients.[85] Mechanically, iron deposition in the brain upregulates Aβ precursor protein (APP) expression.[86] APP is a transmembrane glycoprotein which mediates the production of Aβ through amyloidogenic processing. Neuronal APP is normally processed by α-secretase and γ-secretase in a non-amyloidogenic pathway. However, neurotoxic Aβ peptide is generated when APP is cleaved by sequential action of β-secretase and γ-secretase. Excess intracellular iron upregulates the expression of APP as well as modulates α-secretase-mediated cleavage of APP.[87-89] Further, iron overload induces cognitive impairments by increasing aggregation of Aβ and tau, and hyperphosphorylation of tau,[90-92] whereas amyloid plaque formation in turn may induce free iron and ferritin accumulation in the cerebral cortex area in APP/PS1 transgenic mice.[93] Tau accumulation in NFTs was also found to induce HO-1 expression, which releases ferrous iron by the catabolism of haem and exacerbate oxidative stress.[94-96] In addition, iron chelators such as desferrioxamine, deferasirox and deferiprone, function as ferroptosis inhibitors and have shown potential in pre-clinical and clinical AD models, which indirectly verify that iron and ferroptosis are involved in the pathology of AD.[97, 98]

Brain PLs are extremely susceptible to lipid peroxidation in AD

Different organelles have highly distinct lipid compositions, of all organs of the body, human brain is known to be a lipid-dense organ, second only to adipose tissue. The dry weight of human adult brain is about 60% lipids, which is composed mostly of glycerophospholipids and sphingolipids, as well as a great pool of cholesterol and cholesterol metabolites. Glycerophospholipids and sphingolipids, two important PL subcategories, are key components of all cell membrane, especially for membrane-rich tissue such as grey matter and white matter.[99] PUFA derivatives account for approximately one-third of PLs.[100] The distribution of PUFA in brain PLs is tissue-specific, with white matter abundant in MUFA, while gray matter abundant in PUFAs. Cellular PUFAs are categorized into n-6 PUFA and n-3 PUFA based on the position of the first double bond counting from the methyl carbon atom. The most abundant PUFAs incorporated into cell membrane PLs in mammalian brain gray matter is DHA (22:6n-3) with the longest side-chain and highest degree of unsaturation, and arachidonic acids (AA, 20:4n-6), one of n-6 PUFA.[101] Interestingly, the composition of PUFA of human brain tissue is characterized by age-specific changes. AA methyl esters is roughly equal to DHA methyl esters in cerebral cortex ethanolamine glycerophospholipids in the one-month old infant (16.5% AA and 16.1% DHA). DHA increases with age accompanied by corresponding decrease of AA, and the ratio of DHA/AA is close to approximately 4:1 in 82-year old male (10.3% AA and 33.9% DHA).[102]

PUFA are the most susceptible to peroxidation due to their high degree of unsaturation and play a key role in ferroptosis. Compelling evidence has shown that phosphatidylethanolamine (PE), which contains oxidized forms of AA and adrenic acid (AdA, 22:4n-6) but not DHA is proved to be a key mediator of ferroptotic cell death in cells.[60] It was largely explained by cell-specific differences in lipid profiles. Cancer cells, the cell mode most used in ferroptosis study, are abundant in AA but deficient in DHA. For example, AA levels of membrane PL in ferroptosis sensitive B16 melanoma cells are 5 times higher than DHA levels.[103] In neuroblastoma cells in which DHA levels are slightly less than AA levels, other PUFA-containing PLs, including various diacyl and ether-linked PLs, are oxidized and ferroptotic cell death is induced.[104]

Recent evidence shows that DHA with highly unsaturated structure (six double bonds) is most susceptible to lipid peroxidation and implicated in ferroptotic cell death. For example, Doll et al. reported that n-6 PUFA such as 5,8,11-eicosatrienoic acid (5,8,11-ETE), 8,11,14-ETE,

AA, AdA induced cell death with 5- to 10-fold greater efficacy than n-3 PUFAs such as 11,14,17-ETE, eicosapentaenoic acid except DHA.[105] In acidic tumor environment, DHA is peroxidized and ferroptotic cell death is induced in cancer cells.[106] Our unpublished data also showed that cell apoptosis and necrosis are induced by lipid peroxidation of free unesterified DHA, whereas ferroptotic cell death is induced when DHA is incorporated into membrane PLs and peroxidized. In line with our finding, Ou et al. reported that low-density lipoprotein nanoparticles reconstituted with DHA induce ferroptosis in hepatocellular carcinoma.[107] It is largely explained by the reason that unesterified DHA enters the cell by diffusion or facilitative transporters and is peroxidized before being integrated into membrane PLs, whereas low-density lipoprotein nanoparticles directs DHA along the endolysosomal pathway in the cell and prevent it being peroxidized before being incorporated into membrane PLs, which explains different cell death types induced by different forms of DHA. Overall, human brain tissues abundant in DHA and AA are most susceptible to lipid peroxidation and ferroptosis.

The dysfunction of the GSH/GPX4 axis in AD

Several lines of evidence suggest that altered GSH contributes to various aging-related neurodegenerative disorders, including AD.[108] The neuroprotective role of GSH has been evidenced in various *in vitro* and *in vivo* studies.[109] In blood samples and brain of animal model of AD, decreased GSH and increased glutathione disulphide (GSSG), the oxidized form of GSH, were observed.[110] Bemergo et al. reported that a decrease in erythrocyte GSH levels and GSH/GSSG ratio in AD and mild cognitive impairment (MCI) patients compared with their control subjects.[111] Liu et al. also reported that GSH concentration was significantly decreased in red blood cells from male AD patients as compared with that from age-matched male controls, however, no significant difference of GSH levels in the plasma, white blood cells, or red blood cells between female AD patients and female controls.[112] Importantly, GSH levels were significantly decreased in mitochondrial and synaptosomal fractions of AD and MCI patients compared to age- and postmortem interval-matched controls.[113] In another study, reduced GSH levels were observed in the hippocampus and frontal cortex brain regions in AD and MCI patients with *in vivo* magnetic resonance spectroscopy.[114] These studies suggest that GSH, especially brain GSH concentration is a biomarker for MCI and AD.

GPX4 is the most widely expressed isoform in brain tissue and found predominantly in neurons of the cerebellum, hippocampus and hypothalamus, suggesting that GPX4 may play a protective role against neurodegeneration.[115] Rocha et al. found that polymorphisms in GPX4 are significantly associated with episodic memory and AD in a South Brazilian population.[116] In an *in vivo* study, Hambright et al. reported that Gpx4BIKO mice with conditional deletion of GPX4 in forebrain neurons exhibited deficits in spatial learning, memory function and hippocampal neurodegeneration. Markers associated with ferroptosis were observed in the cognitively impaired Gpx4BIKO mice. The neurodegeneration in Gpx4BIKO mice was ameliorated by small molecular ferroptosis inhibitors such as ferrostain-1 and liproxstatin-1.[117]

Modulation of ferroptosis and their clinical effects of plant-derived dietary antioxidants

The above discussion supports that ferroptosis is implicated in neurodegeneration of AD. Therefore, targeting ferroptosis could be a promising therapeutic strategy for AD. In recent decades, increasing plant-derived dietary antioxidants with diverse biological activities have been gained tremendous attention due to their excellent health benefits. However, there is a general reluctance to launch new clinical trials based on plant-derived dietary antioxidants due to the concerns about their safety, efficacy, and animal mode of action. We then focus on the plant-derived dietary antioxidants which have been studied to assess their pharmacological potential in AD in clinical trials and summarize their anti-AD mechanisms via ferroptosis and their efficacy in treating AD (Table 1 and 2).

Vitamin E (VE)

VE, is the most potent lipophilic chain-breaking antioxidant fat-soluble vitamin consisting of eight different isoforms, including α-, β-, γ-, δ-tocopherol, and α-, β-, γ-, δ-tocotrienol. α-Tocopherol, the most common isoform of VE possesses the most potent biological activity and is directly implicated with human VE deficiency symptoms.[118-120] VE, which is predominantly synthesized in plants, is rich in plant products such as nuts, seeds, plant oils and leafy green vegetables. Considering that VE is exclusively synthesized by photosynthetic organisms, therefore, plant-based food is the primary source of VE.[121, 122] VE is able to pass through the blood-brain barrier and accumulate at therapeutic levels in the areas of the central nervous system, where it functions as a free radical scavenger to prevent lipid peroxidation of polyunsaturated fatty acids in the phospholipid bilayer of cells and lower β-amyloid deposition.[123, 124]

Several pre-clinical studies have been suggested that VE is involved in regulating ferroptotic cell death. Gpx4BIKO mice fed a VE-deficient diet exhibited hippocampal neurodegeneration and locomotor dysfunction, compared with VE-supplemented mice.[117] In another in vitro study, Ren et al. found that treatment with VE significantly inhibited irradiation-mediated ferroptosis of murine hippocampal neuron HT-22 cells and promoted their survival.[125] Zhu et al. also reported that VE inhibited ferroptosis and promoted neural function recovery and tissue repairment in rats with spinal cord injury via down-regulating 15-lipoxygenase.[126] Hinman et al. found that alpha-tocopherol hydroquinone, a specific endogenous metabolite of VE, exhibited more potential ferroptosis role than its parent compound, and inhibited 15-lipoxygenase via reduction of the enzyme's non-heme iron from its active Fe^{3+} state to an inactive Fe^{2+} state. This finding casts doubt on the prevailing model that VE acts predominantly as a non-specific lipophilic antioxidant and suggests that VE is instead a pro-vitamin, with its quinone/hydroquinone metabolites responsible for its anti-ferroptotic activity.[127] These pre-clinical studies suggest that VE can reverse ferroptosis-related neurodegeneration in cell and animal models.

Table 1. List of various compounds that acts as anti-ferroptotic agents for the AD treatment

Classification Compound(s)	Sources	Proposed anti-ferroptotic actions	Cells/model	Key reference
VE	Nuts, seeds, plant oils and leafy green vegetables	VE deficient exacerbated hippocampal neurodegeneration	Gpx4BIKO mice	117
		VE reversed radiation-induced ferroptosis via decreased GSH level and increased MDA, lipid ROS and intracellular iron ion levels	Mouse hippocampal HT-22 cells	125
		VE downregulated 15-lipoxygenase and reversed spinal cord injury-induced ferroptosis	Sprague-dawley male rats	126
Alpha-tocopherol hydroquinone	A specific endogenous metabolite of VE	Inhibiting 15-lipoxygenase via reduction of the enzyme's non-heme iron from its active Fe^{3+} state to an inactive Fe^{2+} state.	Sprague-dawley male rats	127
Resveratrol	Plant sources, such as grapes, blueberries, peanuts, soybeans, pomegranates	Resveratrol pretreatment activated the Nrf2/GPX4 pathway	Mice with spinal cord injury	135
		Resveratrol treatment reduced Fe^{2+} concentrations	Mouse hippocampal HT22 cells	136
		Resveratrol inhibited ferroptosis via the Akt/Nrf2 pathway	PC12 cells	137
		Resveratrol prevented sleep deprivation-induced hippocampal ferroptosis via increasing GPX4, xCT and STING expression	C57BL/6 J mice	138
EGCG	Solid green tea extract	EGCG inhibited the binding of RSL3 to GPX4 instead directly binding to the GPX4 activation site	SH-SY5Y neuronal cells	146
		EGCG upregulated expression of GPX4 and FTH1, downregulated expression of ACSL4 and COX2	Cerebellar granule neurons	147
Curcumin	The rhizomes of the plant Curcuma Longa Linn	Curcumin regulated Nfr2/HO-1 signaling pathway	C57BL/6 J mice	161
Quercetin	Fruits, vegetables, green tea and even in red wine	Quercetin decreased lipid peroxidation and iron deposition in the hippocampus, and upregulated the Nrf2/HO-1 pathway	Type 2 diabetic Goto-Kakizak rats and PC12 cellls	176
		Quercetin modulated microglial M1/M2 polarization, alleviated iron deposition in the whole brain, and increased GPX4 and Nrf2 expression	C57BL/6 J mice and HT22 cells	178
		Quercetin also prevented the ferroptosis of oligodendrocyte progenitor cells by decreasing iron concentration and increasing GSH	Oligodendrocyte progenitor cells	177
Baicalein	The roots of Scutellaria baicalensis	Baicalein reverses the cerebral ischemia-reperfusion-induced ferroptosis via regulating GPX4/ACSL4/ACSL3 axis	C57BL/6 J mice and HT22 cells	186
		Baicalein upregulated the intracellular GSH contents	Dopaminergic CATH cells	188
		Baicalein inhibited 12/15- lipoxygenase enzymatic activity	APP/PS1 mice	189
		Baicalein reduced 15-lipoxygenase, ACSL4; increased GSH	C57BL/6 J mice	187
ALA	Fruits and vegetables	ALA inhibited hyperphosphorylated tau-induced iron overload and ferroptosis	P301S tau transgenic mice	199
		ALA regulated iron metabolism and inhibited the downregulation of GPX4	Parkinson's disease mouse model and PC 12 cells	200, 201

VE: vitamin E; EGCG: epigallocatechin-3-gallate; ALA: alpha-lipoic acid

Table 2. List of clinical trials utilizing combination/conjugate plant-derived bioactive compounds as preventative therapy or treatment in AD

Natural compound	Participants	Intervention	Main results	Key reference
VE+Selegiline	341 patients with moderate AD	2000 IU VE, 10 mg selegiline, both VE and selegiline or placebo daily for 2 years	Treatment with VE or selegiline slowed the progression of disease in patients with moderate AD	130
VE +Memantine	613 patients with mild to moderate AD	2000 IU VE, 20 mg memantine, both or placebo daily for 5 years	Compared with placebo, 2000 IU/day of VE resulted in slower functional decline. No difference between groups receiving memantine alone or memantine + VE	131
VE +Donepezil	790 patients with mild cognitive impairment	2000 IU VE, 10 mg donepezil or placebo, daily for 3 years	VE had no benefit. Donepezil was associated with a lower rate of progression in first 12 months	132
Resveratrol	119 patients with mild to moderate AD	Up to 1 mg resveratrol by mouth twice daily or placebo for 52 weeks	Resveratrol decreases CSF biomarkers, modulates neuro-inflammation and induces adaptive immunity	139
Resveratrol	22 healthy adults	2 doses (250 and 500 mg) of trans-resveratrol in counterbalanced order or Placebo on separate days, after a 45-min resting absorption period, cerebral blood flow and deoxyhemoglobin were assessed	Resveratrol administration resulted in dose-dependent increases in cerebral blood flow and deoxyhemoglobin.	140
Resveratrol + dextrose + malate	39 patients with mild to moderate AD	5 mg resveratrol + 5 mg dextrose + 5 mg malate or placebo twice daily for 1 year	Low-dose resveratrol is safe and well-tolerated, no significant effects on cognitive function and behavior in subjects with mild to moderate AD	141
EGCG	91 patients with mild cognitive impairment	1680 mg green tea extract and l-theanine or placebo for 16 weeks	Green tea extract and l-theanine improved memory and selective attention aa evidenced by brain theta waves were increased significantly in the temporal, frontal, parietal, and occipital areas	153
EGCG	33 elderly participants with cognitive dysfunction	2 g/day of green tea powder or placebo powder for 12 months	Green tea consumption did not significantly affect cognitive function, but prevent an increase of oxidative stress	154
Curcumin	40 non-demented adults	Theracurmin® containing 90mg of curcumin twice daily or placebo for 18 months	Daily oral Theracurmin® may lead to improved memory and attention in non demented adults. Symptom benefits are associated with decreases in amyloid and tau accumulation in brain regions modulating mood and memory	166

VE: vitamin E; EGCG: epigallocatechin-3-gallate; ALA

Table 2. List of clinical trials utilizing combination/conjugate plant-derived bioactive compounds as preventative therapy or treatment in AD (cont.)

Natural compound	Participants	Intervention	Main results	Key reference
Curcumin	60 healthy adults aged 60–85	Longvida® containing 80 mg of curcumin in acute (1 and 3 h after a single dose), chronic (4 weeks) and acute-on-chronic (1 and 3 h after single dose following chronic treatment) treatment	One-hour post-dose, curcumin administration improved attention and working memory. Chronic treatment improved working memory and mood. Acute-on-chronic treatment improved alertness and contentedness.	168
Curcumin	34 patients with AD	1g, 4g of curcumin or placebo once daily for 6 months	1, 4g of curcumin intervention did not demonstrate significant differences in MiniMental state examination scores throughout time or among treats	169
Curcumin	36 patients with mild-to-moderate AD	2 g, 4 g of Curcumin C3 Complex® or placebo daily for 24 weeks	Curcumin was generally well-tolerated, but unable to demonstrate clinical or biochemical evidence of efficacy of curcumin in AD	170
Quercetin	12 older adults aged ≥65 years with slow gait speed and mild cognitive impairment	100 mg of dasatinib and 1250 mg of quercetin for two days every two weeks over 12 weeks	Dasatinib and quercetin treatment was feasible, safe, and improved cognition	182
Baicalein	36 healthy participants	200, 400, and 800 mg baicalein or placebo once daily on days 1 and 10, twice daily on days 3–9,	In dose range of 200–800 mg, multiple-dose oral baicalein administration was safe and well tolerated	192
ALA	61 AD patients with Type 2 diabetes mellitus and 65 AD patients without Type 2 diabetes mellitus	ALA (600 mg/day) in combination with antidementia treatment for 16 months	ALA treatment could be effective in slowing cognitive decline in patients with AD and diabetes mellitus	203
ALA+n-3 fatty acids (fish oil)	39 patients with AD	ALA (600mg), fish oil (3 g/day) containing a daily dose of 675mg DHA and 975 mg EPA, ALA+fish oil or placebo for 12 months	The combination of ALA+n-3 fatty acids slowed cognitive and functional decline in AD over 12 months	204
ALA+ acetylcholinesterase inhibitors	9 patients with AD	600 mg ALA once daily + acetylcholinesterase inhibitors	The treatment led to a stabilization of cognitive functions	205

ALA: alpha-lipoic acid

A meta-analysis by Lopes da Silva et al. reported that plasma VE levels were significantly reduced in AD patients than controls.[128] Some observational studies and placebo-controlled trials showed that VE supplement may potentially prevent the occur of AD or protect against aggression of AD. A study by Basambombo et al. indicated that VE supplements are associated with a reduced risk of cognitive decline.[129] Sano et al. reported that supplementation with 2000 IU of VE slowed the progression of disease in patients with moderately severe impairment from Alzheimer's disease.[130] A double-blind, placebo-controlled, parallel-group, randomized clinical trial by Dysken et al. found that among patients with mild to moderate AD, 2000 IU/d of alpha tocopherol compared with placebo resulted in slower functional decline.[131] However, a multicenter, randomized, double-blind, placebo-controlled, parallel-group study by Ronald et al. found that supplement with 2000 IU VE daily for three years had no benefit in patients with MCI.[132] In addition, a meta-analysis by Farina et al. found no evidence that α-tocopherol given to people with MCI prevents progression to dementia, or improves cognitive function in people with MCI or dementia.[133] These conflicting results suggest that more large, high-quality clinical trials are required to determine whether VE supplements have a potential in decreasing AD risk or slowing down the progression of AD.

Resveratrol

Resveratrol, also known as trans-3,4',5-trihydroxystilbene, is a polyphenol found in various plant sources, such as grapes, blueberries, peanuts, soybeans, pomegranates, and dark chocolate. Resveratrol can react with other chemicals to form new derivatives to increase its use in foods, until now more than 400 products containing resveratrol can be found on the market. Resveratrol has been linked potential health benefits like neuroprotection through its greater antioxidant and anti-inflammatory properties as well as its ability to inhibit the formation of Aβ peptide and neurofibrillary tangles in cell lines and animal models.[134] *In vivo* studies also showed that resveratrol pretreatment inhibited ferroptosis through activating the Nrf2/GPX4 pathway in mice with spinal cord injury and reducing Fe^{2+} concentrations in mouse hippocampal HT22 cells.[135, 136] Resveratrol also ameliorated depression-like behaviors by inhibiting ferroptosis via the protein kinase B (Akt)/Nrf2 pathway.[137] In addition, resveratrol prevented sleep deprivation-triggered cognitive impairment by modulating hippocampal ferroptosis via increasing GPX4, xCT and STING expression.[138] Although *in vivo* and *in vitro* studies show that resveratrol exhibits potential efficacy against AD, the findings from clinical studies are controversial.

Several studies have shown that resveratrol could serve as a potential therapeutic agent to manage the progression of AD. In a randomized, placebo-controlled, double-blind, multicenter 52-week phase 2 trial of resveratrol in individuals with mild to moderate Alzheimer disease, Moussa et al. reported that after 52 weeks, 500 mg resveratrol orally once daily (with a dose escalation by 500-mg increments every 13 weeks, ending with 1000 mg twice daily) was safe and well-tolerated. Simultaneously, resveratrol decreased cerebrospinal fluid human matrix metalloproteinase 9, modulated neuro-inflammation, and induced adaptive immunity.[139] On the contrary, in a randomized, double-blind, placebo-controlled, crossover study on young healthy subjects showed that resveratrol administration resulted in an increase in cerebral blood flow and had no short term effect in cognitive performances.[140] In addition, a randomized, double-blind, placebo-controlled trial conducted by Zhu et al. showed that low-dose oral resveratrol (5 mg) was safe and well tolerated, and after 12 months, low dose of resveratrol had no significant effects on cognitive function and behavior in subjects with mild to moderate AD.[141] Due to the small samples in above-mentioned study, a larger study is required to determine whether low dose resveratrol may be beneficial.

EGCG

EGCG represents the principal bioactive polyphenol from in solid green tea extract. Tea is one of the most consumed beverages worldwide. The annual sale of green tea is estimated to exceed $11 billion globally. In addition, EGCG has been shown to act as a natural antioxidant in foods, because it is water-soluble. Preclinical studies have shown that EGCG has several beneficial properties including anti-oxidant, anti-inflammatory effects as well as neuroprotective effects against neuronal damage and brain edema. *In vitro* studies demonstrated that EGCG reduced the accumulation of Aβ by enhancing endogenous APP proteolysis and decreased nuclear translocation of c-Abl.[142] EGCG was also able to suppress the expression of Aβ-induced TNFα, IL-1β, IL-6, and iNOS, and restored the levels of intracellular antioxidants Nrf2 and HO-1.[143] In addition, experiment animal models of AD suggest that EGCG exerts its neuroprotective effects via suppressing Aβ accumulation, modulating tau pathology and reducing cognitive impairment.[144,145] Similarly, EGCG was found to inhibit ferroptosis inducers-induced ferroptosis by inhibiting the binding of RSL3 to GPX4 instead directly binding to the GPX4 activation site in SH-SY5Y neuronal cells.[146] The neuroprotective function of EGCG was investigated in cerebellar granule neurons as a simulation of spinal cord injury. EGCG inhibited ferroptosis and increased the survival rate of cerebellar granule neurons by upregulating phosphorylation of protein kinase D1, upregulating expression of GPX4 and FTH1, and downregulating expression of ACSL4 and cyclooxygenase 2 (COX2).[147]

Although these encouraging results *in vitro* and *in vivo* studies, clinical trials demonstrating efficacy of EGCG against AD were scare. Some observational studies show an inverse association of tea consumption with the risk of AD. A cross-section study by Shinichi et al. showed that a higher consumption of green tea is associated with a lower prevalence of cognitive impairment in elderly individual over 70 years old.[148] Wang et al. in a prospective cohort study reported that green tea consumption was significantly associated with lower prevalence of all-cause dementia in hypertensive population.[149] Another cross-section study showed that green tea protected against amnestic MCI in the elderly male Han population, but not female green tea consumers.[150] A longitudinal

study showed that high frequency of green tea intake was significantly associated with a lower risk of dementia.[151] However, a longitudinal study by Fischer et al. reported no significant association of green tea with incident AD or memory decline.[152]

Due to confounding and selection bias of observational studies, intervention studies using randomized controlled trials are needed to establish a cause-and-effect relationship between tea consumption and lower risk of dementia. However, clinical intervention studies demonstrating the protective effects of green tea against cognitive impairment or AD are scare. In a randomized, double-blind, placebo-controlled study found that a combination of green tea extract and L-theanine had beneficial effects on cognition in individuals with MCI.[153] Another double-blind, randomized controlled study assessed the effects of green tea consumption on cognitive dysfunction. Green tea consumption of 2g/day for 12 months did not significantly improve cognition function but prevented an increase in oxidative stress in elderly population with cognition dysfunction.[154] Nevertheless, this study has several limitations including a small sample of 27 participants and a short follow-up intervention time. Therefore, long-term intervention and large-sample controlled studies are needed to clarify the effects of normal daily green tea consumption on cognitive dysfunction in the elderly.

Curcumin

Curcumin is a polyphenol compound extracted from the rhizomes of the plant *Curcuma Longa Linn*, also known as turmeric, which belongs to the zingiberaceae (ginger) family. Traditionally, curcumin has been used as a food preservative to treat various ailments in India and China.[155] *In vitro* and *in vivo* studies have shown that curcumin exhibits potentially important biological and pharmacological activities, including anti-inflammatory, antioxidant and neuroprotective properties.[156-158]

Preclinical models have demonstrated a strong potential of curcumin to prevent neurodegenerative diseases through decreasing tau hyperphosphorylation and inhibition of Aβ formation and aggregation.[159, 160] Curcumin was also found to exert its neuroprotective role through suppressing subarachnoid hemorrhage-induced neuronal ferroptosis by regulating the Nfr2/HO-1 signalling pathway.[161] Lei et al. reported that curcumin - polydopamine nanoparticles inhibited neuron ferroptosis by chelating and reducing Fe^{2+} accumulation.[162] In addition, epidemiological data also support the concept that curcumin can prevent neurodegenerative diseases such as AD. For instance, India, with the regular intake of turmeric about 4g/day in their routine diet has been reported to have a lower incidence rate and prevalence of AD.[163]

Contrary to preclinical and epidemiological studies, only a limited number of clinical studies have investigated the effects of curcumin on human cognitive function, and the results of these studies are conflicting. In healthy older population, curcumin administration shows a potential neuroprotective benefit. A double-blind, placebo- controlled trial by Small et al. evaluated the efficacy of Theracurmin®, a compound that contains 90 mg of curcumin in non-demented adults. Theracurmin® was developed using a microparticle and surface-controlled drug delivery system, exhibiting over 30-fold higher bioavailability than conventional curcumin in rats.[164] It has been verified that high plasma curcumin levels can be safely achieved after single administration of Theracurmin® up to 210 mg in healthy volunteers.[165] Small et al. found that daily oral Theracurmin® led to significant memory and attention benefits, suggesting that symptom benefits are associated with decreases in amyloid and tau accumulation in brain regions modulating mood and memory.[166] Similarly, Cox et al. evaluated the effect of Longvida® Optimized Curcumin, a compound that contains 80 mg of curcumin in healthy adults, between 65 and 80 years of age for 12 months. Longvida® capsule encapsulates the free curcumin in a tri-lipid matrix with solid lipid curcumin particle technology, enhancing its solubility, allowing it to survive digestion and enter the bloodstream, target tissues.[167] It was found that one-hour post-dose, curcumin administration improved attention and working memory.[168] However, clinical studies on population with MCI or AD showed no cognitive enhancing effects of curcumin. A pilot trial was conduct by Baum et al.[169] to assess the efficacy of curcumin on a Chinese adult population with progressive cognitive impairment. The intervention group received curcumin (1 g or 4 g) either in capsules or as powder for 6 months and did not demonstrate significant differences in MiniMental state examination (MMSE) scores throughout time or among treats, although increased Aβ1-40 levels and VE were observed. Similarly, a randomized, double blind, placebo-controlled study by Ringman et al. reported that a population with mild to moderate AD received Curcumin 3 Complex®, composing three different constituents (curcumin, bisdemethoxycurcumin and demethoxycurcumin) for 24 weeks. No significant differences in cognitive function, Aβ and tau levels in plasma and CSF were found.[170] Given the limited available clinical studies of the effect of curcumin in AD patient, it needs more clinical trial studies with large sample size and long treatment duration to evaluate the neuroprotective role of curcumin in AD patients.

Quercetin

Quercetin belongs to the flavonoids family, which is found in most of the plants including fruits, vegetables, green tea and even in red wine and has a wide range of biological actions including anti-oxidant, anti-carcinogenic, anti-inflammatory and antiviral activities.[171] The dietary intake of total flavonoids is estimated to be 200-350 mg/day, and the intake of quercetin is 10-16 mg/day.[172] *In vitro* studies demonstrated that quercetin inhibited Aβ fibril formation, tau-fibril aggregation and hyperphosphorylation of tau protein.[173-175] In addition, quercetin protected against diabetic encephalopathy through inhibition of hippocampal ferroptosis, as evidenced by decreased lipid peroxidation and iron deposition in the hippocampus, and upregulated the Nrf2/HO-1 signalling pathway.[176] Quercetin also prevented the ferroptosis of oligodendrocyte progenitor cells by inhibiting the Id2/transferrin pathway accompanied by decreased iron concentration and increased GSH.[177] A recent study reported that quercetin inhibited neuronal pyroptosis and ferroptosis by modulating microglial M1/M2 polarization,

alleviating iron deposition in the whole brain, and increasing GPX4 and Nrf2 expression in atherosclerosis.[178] In another study, it was demonstrated that quercetin and resveratrol likely protected against erastin- and RSL3-induced ferroptosis by inhibiting the iron-catalyzed generation of hydroxyl radicals in mouse hippocampal HT22 cells.[136]

Preclinical *in vivo* studied showed that quercetin improved cognitive and emotional function in mouse models of Alzheimer's disease. Wang et al. reported that long-term treatment with quercetin lessened learning and memory deficits in in the APPswe/PS1dE9 transgenic mouse model of AD.[179] Another study showed that quercetin protected cognitive and emotional function decreases extracellular β-amyloidosis, tauopathy, astrogliosis and microgliosis in the hippocampus and the amygdala in aged 3xTg-AD mice.[180] Administration of quercetin along with daily usage of flavonoid rich fruits also decreased amyloid load and improves behavior in the transgenic mice (APPsw/Tg2576) of AD.[181] Until now, clinical trials investigating the neuroprotective role of quercetin against AD were scare. A pilot study by Millor et al. found that Dasatinib and quercetin treatment was feasible, safe, and improved cognition in older adults aged ≥65 years with slow gait speed and MCI.[182]

Baicalein

Baicalein, a naturally occurring flavonoid primarily derived from the roots of *Scutellaria baicalensis*, a prominent herb in traditional Chinese medicine and is used as dietary supplement in Asia. Baicalein has been traditionally used to treat inflammation, bacterial infections, viruses, and fever. It exhibits a wide range of pharmacological activities, including antioxidant, anticancer, neuroprotective, and cardioprotective properties.[183] Baicalein also exhibited neuroprotective role by suppressing heparin-induced tau aggregation via initializing non-toxic tau oligomer formation.[184] Shi et al. reported that baicalein ameliorated the memory and cognitive deficits in APP/PS mice via regulating gut microbiota.[185] Recent studies have shown that baicalein exert its neuroprotective activity by inhibition of ferroptosis. For instance, Li et al. reported that baicalein reversed the cerebral ischemia-reperfusion injury via anti-ferroptosis, which is regulated by GPX4/ACSL4/ACSL3 axis.[186] Baicalein was also reported to decrease ferroptotic phosphatidylethanolamine oxidation and improved outcome after controlled cortical impact.[187] Long-term treatment of baicalein upregulated the intracellular GSH contents and exerted neuroprotective effects against oxidative stress-induced neuronal damage.[188] In addition, long-term oral administration of baicalein inhibited 12/15-LOX enzymatic activity and reduced Aβ production in APP/PS1 mice.[189] Baicalein can also chelate iron via its 6,7-dihydroxy structure and inhibit iron-induced lipid peroxidation and oxidative stress damage.[190]

Although pre-clinical studies demonstrate the neuroprotective effects of baicalein, up to now, whether baicalein has potential as a novel neuroprotective agent for the treatment of AD remains elusive. Two Phase I clinical trials of baicalein chewable tablets in healthy Chinese subjects have been completed in China so far. A Phase I, randomized, double-blind, single-dose trial of baicalein (100-2800 mg) in 72 healthy Chinese adults investigated the pharmacokinetic properties of baicalein and its main metabolite, bacalin. Single oral doses of 100–2800 mg of baicalein were safe and well tolerated by healthy subjects. Clinical laboratory assessments showed no signs of toxicity in the liver or kidney.[191] Another single-center, double-blind, placebo-controlled, parallel-group study investigated the pharmacokinetic properties, safety and tolerability of baicalein after a multiple-ascending-dose protocol in 36 enrolled healthy participants. In dose range of 200–800 mg, multiple-dose oral baicalein administration was safe and well tolerated. In addition, no serious accumulation of baicalein was observed.[192] As the next step, clinical trials testing the effects of baicalein on the cognitive functions in patients with AD will have to be conducted to test what the actual benefits will be.

Alpha lipoic acid (ALA)

ALA, a naturally occurring disulfide molecule, is mainly found in fruits and vegetables and also can be synthesized in animals and humans' tissues with high metabolic activity such as the heart, liver, and kidney.[193-195] ALA has been widely used in pharmaceuticals and nutraceuticals.

Pre-clinical studies demonstrated promising neuroprotective activity of ALA, due to its universal antioxidant activities, iron chelator properties and anti-inflammatory properties.[196-198] Zhang et al. reported that ALA inhibited hyperphosphorylated tau-induced iron overload and ferroptosis and improved abnormal behavior in P301S tau transgenic mice.[199] ALA also exerts a neuroprotective effect on Parkinson's disease model by regulate iron metabolism through upregulating ferroportin (FPN) and ferritin heavy chain 1 (FTH1) and downregulating iron importer DMT1 accompanied by inhibiting the downregulation of GPX4.[200, 201] L-F001, a multifunctional fasudil-lipoic acid dimer prevents RSL3-induced ferroptosis in HT22 cells by decreasing the total number of intracellular Fe^{2+} and restoring FTH1 as well as GPX4 levels.[202] Consistent with pre-clinical data, several clinical studies have been suggested the potential effects of ALA against cognitive decline in patients with AD. Fava et al. investigated that the effect of ALA treatment (600 mg/day) on cognitive performances in AD patients with diabetes mellitus (61 patients) and without diabetes mellitus (65 patients). The results of this study showed that ALA treatment could be effective in slowing cognitive decline in patients with AD and diabetes mellitus.[203] In addition, a randomized placebo-controlled pilot trial by Shinto et al. evaluated the effects of supplementation with n-3 PUFA alone or n-3 PUFA plus ALA compared to placebo on oxidative stress biomarkers and cognitive decline. 39 subjects were recruited and 34 subjects completed the 12-month intervention. This pilot study found that n-3 PUFA + ALA resulted in less decline of cognition compared to placebo or n-3 PUFA alone. However, the limitation of this study is that the effect of ALA alone on cognitive decline was not evaluated.[204] Another clinical trial by Hager et al. investigated the effects of ALA on cognitive functions in nine patients with AD and related dementias.[205] This study provided supportive evidence of ALA therapy in patients with AD and related dementias. However, further

clinical studies on larger cohorts may be required to determine whether ALA effectively improves cognition in AD patients.

CONCLUSION

Since ferroptosis was coined by Dixon et al. in 2012, a list of studies has shown that ferroptosis is implicated in the occurrence and progression of various human diseases including cancer, cardiovascular and neurodegenerative diseases.[22] It is clear that ferroptosis contributes to the pathology of AD, inhibiting ferroptosis has the potential to prevent or treat AD. Therefore, increasing the understanding of the mechanisms and functions of ferroptosis will facilitate the identification of potential targets for the treatment of AD. Although it remains elusive about why and how lipid peroxidation leads to ferroptotic cell death and the exact mechanisms of ferroptosis in AD occurrence and progression, plant-derived dietary antioxidants have drawn considerable attention due to their multiple targets, multiple mechanisms and relatively safe profiles as ferroptosis inducers or inhibitors. Numerous preclinical studies have shown that plant-derived dietary antioxidants possess enormous chemopreventive and therapeutic potential against AD via suppressing abnormal tau phosphorylation or amyloid plaque formation through regulating ferroptosis signalling pathways. Notably, most abovementioned plant-derived dietary antioxidants have demonstrated conflicting clinical results in regulating cognitive functions in patients with AD except ALA. The pathophysiological and phylogenetic differences between rodents and humans and the major drawbacks of plant-derived dietary antioxidants including low bioavailability, low absorption, quick metabolism and the challenges of blood-brain barrier crossing may contribute to the difference in results between animals and human studies. To resolve these problems, novel formulations of natural compounds are currently designed and used in clinical trials. In addition, given the small sample size and the short duration of most clinical trials, further clinical studies with large sample size and long treatment duration may be required to determine whether plant-derived dietary antioxidants have the treatment effects on AD patients. Notably, AD a heterogeneous disease with a complex pathobiology. It is unlikely that a treatment can be effective in all populations, implying that more targeted subpopulations of AD should be considered, and highlighting that more advanced statistical methods for subgroup identification and evaluations should be used in the analysis of future targeted clinical trials of plant-derived dietary antioxidants. Interestingly, nearly all studied have shown that plant-derived dietary antioxidants have better beneficial effects on cognitive functions in healthy aged population than in population with MCI or AD. It suggests that plant-derived dietary antioxidants may exert their preventive role but not therapeutic role in regulating cognitive functions. Therefore, a plant-based diet that contains natural compounds may lead to potential health benefits in preventing cognitive decline in health elderly population whereas ALA which shows therapeutic potential in preventing decline of cognition of patients with AD in clinical trials may be utilized to treat AD alone or in combination with other agents.

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CONFLICT OF INTEREST AND FUNDING DISCLOSURES

The authors declare no conflict of interest.

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