Recent Advances in Traditional Chinese Medicine Extracts Regulating Ferroptosis to Ameliorate Alzheimer' s Disease: Postprint

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Abstract

Alzheimer' s disease (AD) is a common neurodegenerative disorder in the elderly population, with progressive memory impairment as its typical clinical manifestation. Ferroptosis has emerged in recent years as a potential research direction in biological mechanisms; it is an iron-dependent form of programmed cell death. A substantial body of evidence indicates that AD is closely associated with ferroptosis in the brain; however, the exact mechanism of its involvement in AD remains unclear. It may be induced by disorders of iron metabolism, lipid peroxidation, and amino acid metabolism, thereby affecting iron ion deposition in the brain. To date, active chemical constituents from certain traditional Chinese medicines have been extensively studied, such as Rhodiola, Polygala, Ginkgo biloba, and Poria cocos, which have demonstrated significant effects in targeting ferroptosis for the treatment of AD. In this context, this review systematically elaborates on iron metabolism in the brain, the characteristics of ferroptosis, with particular emphasis on the metabolic regulatory mechanisms of ferroptosis. Additionally, this article discusses the connection between ferroptosis and AD, and enumerates drugs containing active constituents from traditional Chinese medicines that ameliorate AD by inhibiting ferroptosis, aiming to provide reference information for future research and development of ferroptosis inhibitors.

Full Text

Recent Advances in Research on Traditional Chinese Medicine Extracts Regulating Ferroptosis to Improve Alzheimer' s Disease

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Abstract

Alzheimer’ s disease (AD) is a prevalent neurodegenerative disorder in the elderly, characterized clinically by progressive memory impairment. Ferroptosis, an emerging form of iron-dependent programmed cell death, has garnered attention as a potential biological mechanism underlying AD. Accumulating evidence demonstrates a close association between AD and cerebral ferroptosis, though the precise mechanisms remain unclear. Current research suggests that AD pathogenesis may involve iron metabolism disorders, lipid peroxidation, and amino acid metabolism dysregulation, which collectively influence iron deposition in the brain. To date, several active compounds from traditional Chinese medicine—such as *Rhodiola rosea*, *Polygala tenuifolia*, *Ginkgo biloba*, and *Poria cocos*—have been extensively investigated and show remarkable efficacy in targeting ferroptosis for AD treatment. This review systematically delineates cerebral iron metabolism and the characteristics of ferroptosis, with particular emphasis on its metabolic regulatory mechanisms. We discuss the interplay between ferroptosis and AD, and catalog effective traditional Chinese medicine constituents that ameliorate AD by inhibiting ferroptosis, aiming to provide a reference for future development of ferroptosis inhibitors.

Keywords: Alzheimer’ s disease; Traditional Chinese medicine; Ferroptosis; Mechanism of action; Review

1. Literature Search Strategy

A computerized search was conducted across PubMed and CNKI (China National Knowledge Infrastructure) databases for publications from January 2018 to June 2024. Chinese search terms included “iron homeostasis,” “ferroptosis,” “iron metabolism,” “iron overload,” and “Alzheimer’ s disease,” while English search terms comprised “iron homeostasis,” “ferroptosis,” “iron metabolism,” “iron overload,” and “Alzheimer’ s disease.” Inclusion criteria encompassed studies addressing the relationship and mechanisms between iron homeostasis, ferroptosis, iron metabolism, iron overload, and AD. Exclusion criteria comprised irrelevant studies, unpublished data, and inaccessible full-text articles.

2. Iron and Its Metabolism in Brain Cells

Iron is the most abundant transition metal in the brain, participating in numerous cellular processes including mitochondrial function, neuronal myelination, and neurotransmitter synthesis and metabolism. Consequently, iron metabolism requires stringent regulation, as both deficiency and overload can trigger cerebral dysfunction. For instance, iron deficiency during infancy leads to intellectual disability and psychomotor impairment, whereas excessive iron deposition in the aging brain correlates with multiple neurodegenerative diseases, including AD. Cellular iron homeostasis depends on the physiological expression of both iron import (influx) and export (efflux) proteins on the cell membrane. Extensive research has identified blood-brain barrier (BBB) endothelial cells as critical regulators of cerebral iron uptake, which involves pathways such as transferrin/transferrin receptor (Tf/TfR1), ferritin heavy chain (FTH1), lactoferrin-lactoferrin receptor (Lf/LfR), and secreted p97-glycosylphosphatidylinositol-anchored p97 (sP97/GPI-P97). Neurons, oligodendrocytes, microglia, and astrocytes express TfR1 and divalent metal transporter 1 (DMT1) on their membranes, enabling iron uptake via TfR1/DMT1 or DMT1 pathways for both transferrin-bound iron (Tf-Fe) and non-transferrin-bound iron (NTBI). Iron release is subsequently mediated by ferroportin 1 (Fpn1)/ceruloplasmin (CP) and/or Fpn1/hephaestin (Heph) pathways. Iron dysregulation represents a crucial pathological process in AD, and ferroptosis emerges as a novel mechanism linking cerebral iron imbalance to neuronal death.

3. Ferroptosis Mechanisms

3.1 Ferroptosis

Ferroptosis is an iron-dependent, lipid peroxidation-driven form of regulated cell death. Previous studies have demonstrated that AD brain tissues frequently exhibit pathological changes consistent with ferroptosis. Concurrently, elevated ferritin and iron levels have been observed in human AD brain tissues, and postmortem brain samples show a positive correlation between total iron content and the rate of cognitive decline following AD diagnosis. These findings collectively underscore the intimate relationship between ferroptosis and AD. The hallmark features of ferroptosis include specific morphological alterations (mitochondrial condensation, disappearance of cristae, increased bilayer membrane density), iron-dependent accumulation of reactive oxygen species (ROS) and lipid peroxides, depletion of glutathione (GSH), inactivation of GPX4, and a distinct set of regulatory genes.

3.2 Metabolic Mechanisms of Ferroptosis

3.2.1 Iron Metabolism Disorder Iron Metabolism Disorder: Maintenance of iron homeostasis requires normal iron metabolism function, encompassing iron uptake, storage, utilization, and excretion. Iron dysregulation constitutes a hallmark of ferroptosis. Research indicates that iron overload can directly induce ferroptosis both in vivo and in vitro during pathological processes. Enhanced ferritin degradation or suppressed ferritin expression increases the labile iron pool (LIP), heightening cellular susceptibility to ferroptosis. For example, expression levels of hepcidin and ferroportin are significantly reduced in the hippocampus of AD brains. Additionally, low expression of Nedd4 family interacting protein 1 (Ndfip1) may contribute to AD pathogenesis by decreasing DMT1 degradation and increasing iron accumulation. Nuclear factor E2-related factor 2 (NRF2) modulates ferroptosis sensitivity by influencing iron metabolism through suppression of transferrin receptor 1 expression. One study demonstrated that iron can promote AD progression by inducing ferroptosis in microglia and neurons. Iron accumulation is mediated not only by Tau phosphorylation but also by redox cycling between ferrous and ferric iron states, where hyperphosphorylated Tau binds ferric iron to form insoluble aggregates, leading to neurofibrillary tangle formation in AD brains. Furthermore, disrupted iron metabolism causes abnormal elevation of intracellular labile iron, triggering Fenton and Haber-Weiss reactions that generate free radicals and activate ferroptosis. In summary, increased iron uptake or decreased iron storage both affect cellular vulnerability to ferroptosis.

3.2.2 Lipid Peroxidation Lipid Peroxidation: Accumulation of lipid peroxides to lethal levels represents another characteristic feature of ferroptosis. Lipid peroxidation metabolites show co-localization with amyloid plaques and correlate strongly with AD progression. AD pathology is marked by accumulation of lipid ROS and reduced cortical GSH content. Lipid peroxide aggregation constitutes the core of ferroptosis. Lipidomic analyses reveal that polyunsaturated fatty acids such as arachidonic acid (AA) and adrenic acid (AdA) are particularly susceptible to oxidation during ferroptosis. These lipids are regulated by three key synthetic enzymes: ACSL4, lysophosphatidylcholine acyltransferase 3 (LPCAT3), and lipoxygenase (LOX). The lipid peroxidation process catalyzes the production of arachidonoyl-CoA and adrenoyl-CoA, which are subsequently converted by LOX to AA/AdA-PE-OOH. Catabolism generates toxic secondary products such as 4-hydroxy-2-nonenal (4-HNE) or malondialdehyde (MDA). Sustained oxidative reactions then cause irreversible damage to cell membrane and plasma membrane structure and function, leading to pore formation and initiation of neuronal ferroptosis, resulting in neurological injury. Experimental knockout or inhibition of these biosynthetic pathways, as well as direct or indirect suppression of GPX4, impairs clearance of lipid peroxides, causing their intracellular accumulation and triggering ferroptosis.

3.2.3 Amino Acid Metabolism Amino Acid Metabolism: Amino acid metabolism plays a crucial role in ferroptosis, with two key participants being the cystine/glutamine antiporter (system Xc-) and GPX4. Solute carrier family member SLC7A11 constitutes an essential component of system Xc-. GPX4 serves as a critical target in triggering ferroptosis and functions as the core enzyme in the antioxidant GSH system. Depletion of cellular GSH and inactivation of GPX4 mediate lipid peroxidation and participate in ferroptosis, establishing GPX4 as a key regulatory factor. Studies have suggested that GSH levels in the hippocampus and frontal cortex may serve as potential biomarkers for predicting AD. Furthermore, experiments in AD rats have observed decreased expression of ferroptosis key factors GPX4 and SLC7A11, with elevated TfR levels that were ameliorated by Fer-1 treatment, indicating that maintaining normal GSH levels and GPX4 function can suppress ferroptosis. Ferroptosis can be induced by certain small molecules, including erastin and RSL3; notably, RSL3 directly inhibits GPX4 activity, while erastin indirectly reduces GSH and GPX4 biosynthesis by suppressing system Xc-.

4. AD and Ferroptosis

Alterations in cerebral iron levels and distribution are regulated by several key molecules involved in iron transport, storage, and homeostasis, including TfR1, Tf, serum ferritin (SF), and FPN1, which collectively contribute to AD onset and progression. Additionally, AD-related experiments have revealed iron deposition, lipid peroxidation, and GPX4 downregulation, suggesting interactive effects with ferroptosis that likely exacerbate neuronal injury through activation of ferroptotic pathways. Human AD studies employing magnetic resonance imaging have provided evidence for ferroptosis, detecting elevated iron content and reduced tissue integrity in the hippocampus of AD subjects. Iron overload in brain tissue impairs cellular antioxidant capacity and triggers massive accumulation of lipid reactive oxygen species (ROS) in brain cells, ultimately causing catastrophic oxidative damage to sensitive subcellular structures and initiating ferroptosis. Furthermore, evidence indicates that elevated cortical iron may bind to Aβ, accelerating clinical AD progression.

Animal models of AD have yielded additional evidence for ferroptosis. GPX4, a key regulator of ferroptosis, participates in suppressing lipid peroxidation, and administration of the ferroptosis inhibitor liproxstatin-1 has been shown to alleviate neurodegenerative changes and inflammation in GPX4 brain-specific knockout mice, suggesting that ferroptosis represents an important neurodegenerative mechanism in AD and related disorders. Moreover, studies in male Wistar rats induced with A\$ $25 - 35 havedemonstratedthatbothferroptosisandnecroptosiscontributetoA$ \$ neurotoxicity through mGLUR5 and STIM proteins, validating that the ferroptosis pathway lies upstream of necroptotic phenomena in Aβ toxicity. In vitro AD models have identified NOX4 as an upstream molecular target of lipid peroxidation-derived ferroptosis in damaged astrocytes. Elevated NOX4 promotes ferroptosis by accumulating 4-HNE and exerting morphological cytotoxicity that impairs mitochondrial metabolism. Additionally, single-cell RNA sequencing (scRNA-seq) analyses of multiple cells from AD patients and healthy controls have revealed significant alterations in three cell clusters —oligodendrocytes, astrocytes, and oligodendrocyte precursor cells (OPCs)— in AD, with identification of two ferroptosis-related hub mRNAs (FTH1 and SAT1) in astrocytes. FTH1 is responsible for intracellular iron storage and metabolism, while SAT1 induces lipid peroxidation and triggers ferroptosis under ROS-induced stress. Furthermore, ferroptosis inhibitors have proven effective in reducing neuronal death and neurological dysfunction caused by

Aβ aggregation. Collectively, these findings demonstrate that AD is closely associated with cerebral ferroptosis, and targeting ferroptosis may offer novel therapeutic insights for AD treatment.

5. Effects of Natural Active Ingredients from Traditional Chinese Medicine on Ferroptosis in AD

Traditional Chinese medicine extracts primarily regulate ferroptosis-related pathway cascades through antioxidant, anti-inflammatory, autophagy-promoting, and neuroprotective effects, thereby inhibiting ferroptosis and ameliorating AD (Table 1).

5.1 Salidroside (Sal)

Salidroside (Sal) is a bioactive compound extracted from *Rhodiola rosea* with antioxidant, anti-inflammatory, autophagy-promoting, and neuroprotective properties. Studies have shown that neuronal ferroptosis and CD8 T cells contribute to cognitive impairment in SAMP8 mice. Sal administration reduces Aβ accumulation and iron deposition, decreases TFR1 protein expression, upregulates SLC7A11 protein expression, and activates the Nrf2/GPX4 axis to alleviate neuroinflammation and oxidative stress, improve mitochondrial ultrastructure, and reduce CD8 T cell infiltration and microglial overactivation, thereby mitigating cognitive deficits and ameliorating neuronal injury and ferroptosis. Additional experimental studies have demonstrated that Sal may exert neuroprotective effects by activating the Nrf2/HO-1 signaling pathway to attenuate neuronal ferroptosis. Sal intervention enhances HT22 cell viability, reduces neuronal damage, improves mitochondrial membrane density and potential, decreases intracellular iron ions, reduces ROS production, lowers MDA levels, increases SOD activity, downregulates ferroptosis-related protein expression, and reduces hippocampal ferroptosis in mice.

5.2 Forsythiaside A (FA)

Forsythiaside A (FA) is isolated from the dried fruits of *Forsythia suspensa* and exhibits notable pharmacological properties including anti-inflammatory, hepatoprotective, antiviral, and neuroprotective effects. Recent research on FA for AD treatment via ferroptosis regulation has gained momentum. Studies in APP/PS1 double-transgenic AD mice have observed that FA administration reduces cerebral Aβ deposition and p-tau levels, suppresses astrocyte activation, decreases iron deposition and lipid peroxidation, activates the Nrf2/GPX4 axis, diminishes pro-inflammatory cytokine secretion, alleviates neuroinflammation, enhances cell viability, and strengthens dopaminergic signaling, thereby improving memory and cognitive impairment.

5.3 Paeoniflorin (Pae)

Paeoniflorin (Pae) is the principal active component extracted from the dried roots of *Paeonia lactiflora*, possessing diverse biological effects including anti-inflammatory, anticancer, neuroprotective, and immunomodulatory activities. In APP/PS1 AD model mice, Pae specifically binds to p53, mitigates oxidative stress injury, increases superoxide dismutase (SOD) expression, reduces iron ions in brain tissue, participates in negative feedback regulation of iron oxidation, suppresses ferroptosis, decreases neuronal damage, alleviates apoptosis, and ultimately ameliorates AD symptoms.

5.4 Icariin (ICA)

Icariin (ICA) is extracted from the dried stems and leaves of *Epimedium* species and exhibits anti-inflammatory, antitumor, cardioprotective, osteogenic, and neuroprotective effects. Research demonstrates that ICA reduces iron content in the brain, increases JC-1 polymer levels, elevates the polymer/monomer ratio, and resists oxidative damage. Moreover, MDM2 has been identified as a potential common target of ICA in AD and ferroptosis. ICA may activate the PI3K/AKT pathway to inhibit Tau hyperphosphorylation at Ser396, Ser404, and Thr205 sites, thereby reducing A$ $25-35-induced PC12 cell apoptosis. Overall, ICA alleviates neuronal ferroptosis and improves neurological injury in AD mice by suppressing mitochondrial lipid peroxidation damage.

5.5 Tetrahydroxy Stilbene Glucoside (TSG)

Tetrahydroxy stilbene glucoside (TSG) is a bioactive compound extracted from *Polygonum multiflorum* with anti-inflammatory, antioxidant, hepatoprotective, anti-aging, and neuroprotective properties. Experimental studies in APP/PS1 mice have investigated ferroptosis-related proteins and enzymes following TSG administration, revealing activation of GSH/GPX4/ROS and Keap1/Nrf2/ARE signaling pathways. TSG improves lipid metabolism, lipophagy, protein processing, ferroptosis, metal ion binding, and regulates expression of related genes, restores mitochondrial function, modulates oxidative stress and inflammatory responses, promotes cell survival, and reduces Aβ deposition. In essence, TSG ameliorates AD through glutathione peroxidase-related ferroptosis modulation.

5.6 Senegenin (Sen) and Tenuifolin (TEN)

Senegenin (Sen) is the primary bioactive component isolated from the dried roots of *Polygala tenuifolia*, exhibiting diverse pharmacological activities including anti-inflammatory, antioxidant, anti-apoptotic, antidepressant, and neuroprotective effects. In PC12 cell models induced with A$ $25 - 35, Sentreatmentreducesoxidativedamage, improveslipidmetabolism, decreasesferroptosis-relatedproteinexpression, reversesmitochondrialdepolarization, andpreservesmitochondrialultrastructural
35-induced ferroptosis. Tenuifolin (TEN) represents another active constituent

of *Polygala tenuifolia*. Research shows that TEN influences neuronal transmission and synaptic plasticity, controls apoptosis and calcium signaling, reduces m-calpain expression, and maintains calpain system stability. By suppressing oxidative stress and ferroptosis in HT-22 cells, TEN promotes cell survival, increases synaptic protein expression, inhibits hippocampal neuronal apoptosis, and thereby improves memory impairment in mice. In summary, TEN may prevent AD-like phenotypes by activating multiple signaling pathways including SLC7A11/GSH/GPX4.

5.7 Ginkgolide B (GB)

Ginkgolide B (GB) is an active component extracted from *Ginkgo biloba* leaves with anti-inflammatory, antioxidant, anti-apoptotic, and neuroprotective properties. Experiments in senescence-accelerated P8 (SAMP8) mice have shown that GB effectively ameliorates cognitive dysfunction and AD-related pathologies, including oxidative stress, neuroinflammation, and Nrf2/GPX4 pathway-mediated ferroptosis. Additionally, proteomic analysis of A$ $1-42-$
$inducedcellinjurytreatedwithGBrevealedthatactivationofthePSEN2/SPP1/SLC7A11pathwayregulatesbo$
42 oligomers, and demonstrates neuroprotective effects against cell injury.

5.8 Berberine (BBR)

Berberine (BBR) is a natural alkaloid isolated from *Coptis chinensis* with anti-inflammatory, antitumor, lipid-lowering, hepatoprotective, gut microbiota-modulating, and neuroprotective effects. Recent studies have shown that BBR administration can influence abnormal iron accumulation in the brains of 3×Tg-AD model mice. Experiments have observed that BBR reduces cerebral Aβ plaques, hyperphosphorylated tau protein, neuronal loss, and lipid peroxide levels, improves mitochondrial damage, and attenuates ferroptosis-related protein expression, likely by modulating the AMPK/GSK3β/Nrf2 pathway to suppress ferroptosis.

5.9 Sennoside A (SA)

Sennoside A (SA) is a bioactive component isolated from senna leaves with laxative, anti-obesity, antitumor, anti-inflammatory, gut microbiota-modulating, and neuroprotective properties. An experimental study in APP/PS1 mouse AD models validated that SA improves cognitive function, attenuates histopathological damage and hippocampal apoptosis, eliminates AD-induced high Fe2+ content in the mouse hippocampus, ameliorates GSH depletion, and reverses pro-inflammatory cytokine and protein levels. SA also alleviates LPS-induced BV2 cell apoptosis, ferroptosis, oxidative stress, and inflammation by reducing TRAF6-NF- B activation.

5.10 1,6-O,O-Diacetylbritannilactone (OABL)

1,6-O,O-Diacetylbritannilactone (OABL) is an active constituent isolated from *Inula britannica*, representing a novel agent with potential anti-neuroinflammatory activity. OABL exhibits favorable blood-brain barrier permeability and low cytotoxicity, demonstrating neuroprotective effects against oxidative apoptosis and ferroptosis in cellular experiments and improving cognitive impairment in 5xFAD mice. By suppressing NF- B signaling pathway activation, OABL inhibits astrocyte proliferation and microglial activation, exhibits effective anti-inflammatory properties, restores mature spine numbers in the hippocampus and cortex, alleviates synaptic neuronal damage and oxidative stress, and thereby suppresses ferroptosis.

5.11 Eriodictyol (ED)

Eriodictyol (ED) is a natural flavonoid compound found primarily in citrus fruits and the peels of certain Chinese herbs, with anti-inflammatory, antioxidant, hepatoprotective, anticancer, free radical-scavenging, and neuroprotective properties. Research has shown that ED can inhibit Aβ aggregation and Tau phosphorylation in APP/PS1 mouse brains, protect mitochondrial function, maintain cellular iron balance by reducing iron influx and increasing iron efflux, suppress lipid peroxidation damage and ferroptosis, and improve cognitive deficits in aged mice. Experiments demonstrate that ED alleviates erastin-induced cell injury, promotes HT22 cell viability, modulates GPX4/SLC7A11 expression and iron metabolic homeostasis, thereby achieving neuroprotection. Additionally, ED may exert anti-ferroptotic effects by activating the Nrf2/HO-1 signaling pathway, ameliorating memory impairment and AD-like pathological changes.

5.12 Epigallocatechin Gallate (EGCG)

Epigallocatechin gallate (EGCG) is a natural polyphenol isolated from green tea leaves with extensive pharmacological capabilities, including anti-inflammatory, anticancer, anti-apoptotic, free radical-scavenging, and neuroprotective effects. EGCG functions as an antioxidant that inhibits APP translation and/or stimulates sAPPα secretion, modulates intracellular iron pools, induces non-amyloidogenic sAPPα release through PKC activation, and suppresses Aβ peptide generation. As an iron chelator, EGCG directly activates the hypoxia-inducible factor 1α (HIF-1α) pathway, which depends on the activity of iron-dependent enzymes HIF-prolyl-4-hydroxylases (HIF-P4Hs). EGCG eliminates excess iron from the brain, preventing its accumulation under oxidative stress conditions, reduces Tau hyperphosphorylation and aggregation, and promotes the non-amyloidogenic processing pathway of APP, thereby preventing Aβ formation and subsequent accumulation.

5.13 Curculigoside (CUR)

Curculigoside (CUR) is a natural active substance extracted from the rhizomes of *Curculigo orchioides*, possessing anti-inflammatory, antioxidant, anti-apoptotic, antidepressant, immunomodulatory, anti-osteoporotic, and neuroprotective properties. Oral administration of CUR alters ferroptosis-related marker levels in neurotoxicity induced by okadaic acid and scopolamine, thereby protecting neurons. By activating the GPX4/SLC7A11 pathway, CUR alleviates iron-induced lipid peroxidation, enhances neuronal viability, modulates mitochondrial dysfunction, reduces ferroptosis in the hippocampus and cortex of AD mice, and improves cognitive impairment in AD model mice. Additional data indicate that CUR exhibits strong neuroprotective effects in vitro, reducing Tau oligomerization and suppressing neurodegenerative changes triggered by oxidative agents H2O2 and Fe3+ toxicity.

5.14 Chrysophanol (CHR)

Chrysophanol (CHR) is an effective monomer extracted from *Rheum palmatum*, demonstrating significant antitumor, hepatoprotective, anti-inflammatory, anti-apoptotic, and neuroprotective properties. In A$ $25-35-induced AD rat models, CHR’ s therapeutic effects likely operate through activation of the GSH/GPX4 pathway, reducing lipid peroxides, ferroptosis levels, and hippocampal neuronal injury while improving learning and spatial memory. Furthermore, CHR ameliorates mitochondrial pathological damage, protects and restores neuronal ultrastructural integrity, and enhances cell viability. These findings suggest that CHR exerts protective effects by reducing ferroptosis levels in AD injury models.

5.15 Water Extract of Moschus (WEM)

Water extract of moschus (WEM) is an effective component extracted from the subumbilical secretions of *Moschus berezovskii* Flerov, with cardioprotective, anti-inflammatory, antioxidant, anticancer, and neuroprotective properties. Experiments using HT22 cell models to investigate ferroptosis in AD suggest that the underlying mechanism may involve activation of the Keap1/Nrf2 pathway to reduce accumulation of related lipid peroxides, prevent intracellular iron accumulation, and decrease ROS production, thereby inhibiting ferroptosis.

5.16 Pachymic Acid (PA)

Pachymic acid (PA) is an effective component extracted from *Poria cocos*, possessing antioxidant, antitumor, autophagy-inducing, and neuroprotective pharmacological activities. Related experiments investigating PA’ s effects on cognitive impairment in AD rats showed that PA treatment effectively improved cognitive dysfunction, reduced abnormal iron deposition in hippocampal tissue, and these effects could be reversed by Nrf2 inhibitors. This demonstrates that PA suppresses ferroptosis via activation of the Nrf2/SLC7A11/GPX4 signaling pathway, thereby ameliorating hippocampal neuronal pathological damage and cognitive impairment in AD rats.

6. Summary and Outlook

Several ferroptosis-specific inhibitors have demonstrated potential clinical benefits in clinical trials, improving AD to varying degrees. Representative metal ion chelators such as deferoxamine (DFO) improve learning and memory abilities in AD animal models when administered intranasally, likely through direct iron chelation, HIF-1α activation, or GSK-3β inactivation via phosphorylation. Another representative ferroptosis inhibitor, ferrostatin-1 (Fer-1), effectively inhibits production of cytosolic and lipid ROS, protecting HT-22 cells from oxidative toxicity. Although these drugs show some clinical efficacy in AD treatment, their long-term therapeutic effects and stability remain unclear as newly synthesized agents. The specific targets and mechanisms underlying their involvement in AD ferroptosis require further elucidation. Additionally, long-term clinical observation is needed to determine whether they disrupt essential iron-dependent physiological functions and whether they remain safe and effective in AD patients with comorbidities.

Furthermore, certain traditional Chinese medicine formulas also regulate ferroptosis to improve AD symptoms. The icariin-astragaloside-puerarin (YHG) combination, composed of active monomers from *Epimedium*, *Astragalus*, and *Pueraria*, improves learning and memory in APP/PS1 mice, reduces cerebral senile plaque deposition, and alleviates neuronal ferroptosis by enhancing amino acid metabolic pathways and antioxidant capacity. Suanzaoren Decoction can alleviate ferroptosis and improve cognitive impairment in AD mice by activating the DJ-1/Nrf2 signaling pathway, thereby mitigating Aβ deposition, neuronal loss, and synaptic damage. However, compared to single active ingredients, clinical application of formulas faces challenges in ensuring effective drug concentrations and convenient administration. Currently, experimental research predominantly focuses on single herbs and their main active components, with limited basic research on formulas, such as pharmacodynamic material basis, drug metabolism component analysis, and in-depth mechanistic investigation in AD. Clinical studies have primarily concentrated on observing therapeutic efficacy in single neurological disorders, with insufficient mechanistic research and a lack of large-scale, multicenter, high-quality randomized controlled trials.

Iron is the most abundant metal element in the human brain and an essential substance for maintaining metabolism and life activities. Its excessive accumulation in the brain can trigger ferroptosis. Cerebral ferroptosis in AD patients has been a research focus in recent years. Cells undergoing ferroptosis exhibit increased cytosolic ROS and lipids, accompanied by reduced mitochondrial volume and increased membrane density. Previous studies clearly suggest that ferroptosis may play an important role in AD onset and progression. However, given that related research remains in its infancy, future efforts must identify optimal neuroprotective anti-ferroptotic targets that can reduce ferroptosis without disrupting iron homeostasis physiological functions. Previous drug development targeting Aβ has failed in clinical trials; ferroptosis as a new potential target opens avenues for novel AD therapeutics. Currently, first-line Western medicines can improve AD symptoms to some extent, but therapeutic effects vary among individuals, fail to reduce or prevent AD-induced neuronal damage, cannot reverse disease progression, and are associated with adverse reactions and drug resistance issues, yielding unsatisfactory clinical efficacy. In this context, this article systematically introduces a series of traditional Chinese medicines —such as *Rhodiola rosea*, *Polygala tenuifolia*, *Ginkgo biloba*, and *Poria cocos* —that target ferroptosis for AD treatment, demonstrating significant efficacy and minimal adverse effects. Future research should continue to refine the precise mechanisms of ferroptosis in AD pathogenesis, enrich corresponding clinical trial validation, and conduct more experimental studies on traditional Chinese medicine formulas for AD prevention and treatment via ferroptosis modulation. Additionally, most mechanistic studies of traditional Chinese medicine against AD remain at the in vitro and animal experimental stages; future exploration of experimental models for syndrome differentiation and treatment in traditional Chinese medicine is needed to better leverage its distinctive advantages.

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