Multiple Roles of Paeoniflorin in Alzheimer’s Disease

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Alzheimer’s disease (AD) is a degenerative disease of the central nervous system that occurs in the presenile and elderly. It will show short-term memory degradation, speech repetition, slow response, language function degradation, obvious decline in understanding and expression ability, and so on. The pathological manifestations were diffuse atrophy of cortex, enlargement of ventricle, and widening of sulcus gyrus [1, 2]. β-Amyloid protein (Aβ) deposition and hyperphosphorylated tau nerve fiber tangles are typical pathological features of AD [3, 4]. At present, there is no specific therapy for the treatment of Alzheimer’s disease; acetylcholinesterase inhibitors are commonly used in clinical treatment and the effectiveness of more treatment methods needs to be further verified.

Along with AD, traditional Chinese medicine (TCM) is also coming into view. The field of TCM shows unique potential and advantages, such as multitarget, multi-approach, and multilevel. In recent years, TCM prescriptions such as Dihuang Yinzi [5], Banxia Baizhu Tianma Tang [6], Danggui Shaoyao San [7], and Kaixinsan [8] have been used to treat AD, while Radix ginseng-Schisandra chinensis herb pair [9], Astragalus Radix-Ligustri Lucidi Fructus herb pair [10], Danshen-Chuanxiong herb pair [11], Rehmanniae Radix Praeparata-Radix Polygomi Multiflori herb pair [12], Radix Polygomi Multiflori-Acori Tatarinowii Rhizoma herb pair [13], and other traditional Chinese medicine pairs have been used to prevent and treat AD.

The monomer components extracted from TCM have become a new research hotspot because of their high efficiency, low toxicity, strong specificity, multi-target, and other characteristics, which can play a role in the treatment of AD in multiple ways. TCM monomer components are mainly divided into alkaloids, phenylpropanoids, flavonoids, saponins, terpenoids, glycosides, and so on. At present, the studies on the therapeutic mechanism of AD are mainly focused on berberine [14–16], evodiamine [17], icariin [18, 19], forsythoside [20], ferulic acid [21], osthole [22, 23], triptolide [24], resveratrol [25], and rhynchophylline andisorhynchophylline [26]. However, there has been a lack of systematic review and research on the relationship between a component of Radix Paeoniae and AD.

Radix Paeoniae Alba is the dried rhizome of Ranunculaceae plant Paeonia lactiflora Pall. It is usually picked in summer and autumn and stir-fried or roasted until yellowish...
in order to be used as medicine. It is recorded in Shennong’s Classic of the Materia Medica, firstly. As one of the traditional Chinese herbal medicines, it is bitter, sour in flavor, and slightly cold in nature, which is mainly reflected in the therapeutic effects of astringing yin and stopping sweating, nourishing blood and regulating menstruation, softening the liver and relieving pain, restraining liver Yang, and so on.

Paeoniflorin (PF), one of the major components of Radix Paeoniae extract, has been clinically used in China and other East Asian countries for possession of antidementia properties and the treatment of neurodegenerative disease. Its molecular formula is C_{23}H_{26}O_{11} (Figure 1). Many studies indicate that PF has the important function of regulating protein, anti-inflammation, antioxidation, antiapoptosis, protecting glial cells, and so on. This review focuses on the latest progress in the role and mechanism of PF in AD and provides a novel perspective on clinical application.

2. Regulatory Protein

2.1. Reduction of Excessive Deposition of Aβ. The pathological changes of AD include the deposition of insoluble Aβ in extracellular and the accumulation of tau protein in intracellular nerve fiber tangles [27, 28]. AD is a neurodegenerative disease related to age and the toxic form of Aβ peptide. The toxic form of Aβ peptide increases with age, and abnormal folding eventually accumulates to form senile plaque (SP) [29, 30]. PF mediates neuroprotective effects such as reduction of neuroinflammation, reduction of amyloid β plaque load, and decreased expression of IL-1β and TNF-α in a transgenic mouse model of AD by activating adenosine A₂R [31]. PF is confirmed to inhibit the phosphorylation of NF-κB and increase the protein expression of kappa B-α and Aβ degrading enzymes to reduce the excessive deposition of Aβ [32].

Research shows that heat shock protein-16.2 (hsp-16.2) plays a significant role in the clearance of misfolded and unfolded proteins in Caenorhabditis elegans and PF can increase the expression of hsp-16.2 in the AD model of C. elegans induced by Aβ1–42 to clear Aβ, delaying C. elegans paralysis caused by the accumulation of Aβ, significantly [33]. On the contrary, PF was thought to treat AD not by removing Aβ and its fibrous plaques but by inhibiting the production of Aβ to reduce the aggregation of Aβ to form fibrous plaques in the experimental rat model [34]. Therefore, the specific mechanism of the influence of PF on Aβ is still controversial and needs to be further explored.

2.2. Inhibition of Abnormal Phosphorylation of Tau Protein. Tau, as a microtubule-associated protein, is the main neuropathological marker of AD [35]. Neurofibrillary tangle (NFT) is formed by hyperphosphorylated tau accumulation, and extracellular amyloid plaques are composed of Aβ [36]. In addition to participating in the formation of neurofibrillary tangles, the accumulation of hyperphosphorylated tau can also lead to neuronal dysfunction and synaptic damage. It is also one of the reasons why CSF and blood tau phosphorylated at threonine could be used as a biomarker for Alzheimer’s disease and for the prediction of cognitive decline [37]. Intracellular MAPT/tau accumulation induced by macrophage/autophagy deficiency is a landmark pathological feature of AD [38], while the autophagy-lysosomal pathway (ALP) is the main pathway for clearance for tau in neurons [39]. Tau can be degraded through the autophagy mTOR pathway, thus relieving the symptoms of AD [38]. The regulation of autophagy can degrade hyperphosphorylated tau to some extent. While PF antagonizes the calpain/Akt/glycogen synthase kinase 3β (GSK-3β) signal pathway, autophagy is stimulated. And, the phosphorylation/activation of GSK-3β is enhanced by autophagy stimulation, resulting in the subsequent hyperphosphorylation of tau [40]. Research showed that IRS-1 and its downstream effector molecules can participate in tau protein hyperphosphorylation. PF pairs prevent tau hyperphosphorylation and protect cognitive impairment by restoring SOCS2/IRS-1 signal pathway [41] (Figure 2 and Table 1).

3. Protection of Neurons

3.1. Inhibition of Inflammatory Response Associated with TNF-α and IL-1β. The inflammatory response of the central nervous system (CNS) is considered to be a very complex defense mechanism. Chemokines secreted by CNS cells, such as TNF-α and IL-1β, which are involved in the mechanism of inflammation, may play a variety of important roles in AD [42–45]. PF exerts neuroprotective effects such as decreased expression of IL-1β and tumor necrosis factor-alpha (TNF-α) and reduction of neuroinflammation in 5XFAD mice by activating adenosine A₁R [31]. Research suggested that inflammation-induced overexpression of SOCS2 can lead to cognitive dysfunction. PF can reduce cognitive dysfunction via regulating SOCS2/IRS-1 signal transduction and blocking tau hyperphosphorylation. Meanwhile, Paeoniflorin can decrease the contents of TNF-α and IL-1β in the hippocampus to reduce inflammation [42]. The involvement of the translocator protein 18 kDa (TSPO) is a biomarker of neuroinflammation in vivo [46, 47]. The neuroprotective effect of PF on neurodegenerative diseases such as AD may be mediated by TSPO and its downstream neurosteroids [48]. PF is confirmed to inhibit TNF-α and IL-1β and the

Figure 1: Chemical structure of Paeoniflorin.
activity of NLRP3 inflammasome to relieve inflammatory reaction [49]. PF can downregulate the protein expression of inducible nitric oxide synthase and cyclooxygenase-2, inhibit the NO production of C6 glial cells induced by A\(\beta\)\(_{25–35}\), and has a protective effect on A\(\beta\)-mediated neuroinflammation [32].

The increase of chemokine level can make more microglia aggregate to A\(\beta\). PF can inhibit the secretion of proinflammatory mediators IL-1\(\beta\), IL-6, and TNF-\(\alpha\) and chemokine CCL2 and CXCL1 by microglia induced by A\(\beta\)\(_{1–42}\) and then treat AD [50].

3.2. Inhibition of Inflammatory Response Associated with DHA Metabolic Signal Pathway. Docosahexaenoic acid (DHA) is an essential high unsaturated fatty acid for brain nutrition, which is beneficial to the growth and development of brain nerve conduction and synapse [51]. Arachidonic acid (ARA) produces PG (prostaglandin), LT (leukotriene), or TX (thromboxane) under the action of COX and 5-LOX. These three active substances have obvious proinflammatory effects. In addition, DHA can produce NPD1 with anti-inflammatory activity and neuroprotective effect under the action of 15-LOX. Interestingly, although DHA and ARA are the main unsaturated fatty acids in the brain, DHA can competitively inhibit the synthesis of LT by ARA, such as LTA\(_4\), LTB\(_4\), TXB\(_2\), and other proinflammatory substances, and then play their own anti-inflammatory effects. On the one hand, Danggui Shaoyao San upregulated the expression of 15-LOX in the DHA metabolic pathway to increase the content of NPD1 in the brain; on the other hand, it downregulated the metabolic enzymes COX family and 5-LOX, thus reducing the proinflammatory activity of PG and LTA\(_4\), LTB\(_4\), and TXB\(_2\) (Figure 3). The therapeutic effect of Danggui Shaoyao San on AD is related to PF [52], and its deeper mechanism needs to be further verified.

3.3. Antioxidant Stress Injury. Oxidative stress and mitochondrial function have long been considered to play a key role in neurodegenerative diseases including AD [53, 54]. Treatment with PF significantly alleviates the degree of oxidative stress as exhibited by the reduction of glutathione.
Improving the cognitive impairment of AD transgenic mice by paeoniflorin and danggui shaoyao san. The solid line represents promotion and the dashed line represents inhibition.

**Figure 3: DHA metabolic signal pathway related to paeoniflorin and danggui shaoyao san.**

(GSH) and superoxide dismutase (SOD) activity. Treatment with PF also significantly alleviates mitochondrial dysfunction as exhibited by increasing cytochrome c oxidase activity and ATP synthesis. PF can improve cognitive impairment and the defect of insulin signal transduction by upregulating the expression of P-PI3K and P-Akt protein and downregulating the expression of P-IRS-1 protein [55].

Reactive oxygen species (ROS) is a natural by-product containing oxygen, which plays a vital role in cell signal transduction. When the redox-active metal ions in the body combine with $\text{A}\beta$, it can catalyze the production of ROS. The increase of ROS level may cause serious damage to the $\text{A}\beta$ peptide itself and other proteins [56–58]. Danggui Shaoyao San (DSS) can significantly reduce the contents of ROS and increase the activities of GSH and SOD in the hippocampus and cortex of APP/PS1 mice, which plays a role in improving the state of oxidative stress in the brain, which is closely related to PF [52].

### 3.4. Reduction of Apoptosis

Apoptosis is widely known as programmed cell death that can be triggered by both intracellular and extracellular signals, which can effectively remove damaged cells, such as DNA damaged cells and mitochondrial oxidative phosphorylation damaged cells [59, 60]. MKK4 is a kind of stress-activated protein kinases (SAPKs), which can activate JNK1 and JNK2 at the same time, regulate transcription factors, and finally participate in the regulation of other cellular processes, such as proliferation, differentiation, and suppression of metastases [61, 62].

Bcl-2 family proteins are the main regulators of modulating cell death and survival, which are divided into two categories: the antiapoptotic genes and proapoptotic genes. Bcl-2-associated X protein (Bax) is an important member of the Bcl-2 family, which can activate a series of downstream genes and induce apoptosis by antagonizing Bcl-2 [63]. Meanwhile, the caspase family and Bcl-2 family play significant roles in the process of apoptosis [64]. PF is proved to improve the cognitive impairment of AD transgenic mice by increasing the Bcl-2/Bax ratio, reducing caspase-3 activity, and inhibiting apoptosis [65]. PF can modulate the Bcl-2/Bax ratio and downregulate cleaved-caspase-3 levels via inhibition of MKK4-JNK signaling pathway to suppress TBTC-induced apoptosis and damage on neurons and treat eventually neurodegenerative diseases such as AD [66]. This is listed in more detail in Table 2.

### 4. Protection of Neuroglial Cells

#### 4.1. Inhibition of Activation of Microglia

The central nervous system (CNS) consists of two broad categories of cells: neurons and neuroglial cells. Microglia are the main resident immune cells of the brain and the innate immune cells of the CNS of myeloid origin, which together with oligodendrocytes, astrocytes, and ependymal cells form the neuroglial cells [67, 68]. Studies have shown that microglia account for 5–12% of central nervous system cells [69]. The dominant view is that microglia mainly originate from bone marrow hematopoietic stem cells in mesoderm [68]. It is also believed that microglia originated from erythromyeloid progenitor cells in the embryonic yolk sac [70]. Its main function is to eliminate microbes, phagocytize necrotic or apoptotic cells, protein aggregates, redundant synapses, and other antigens and particulate that may endanger the CNS [71]. Some study results showed that PF can reduce the overexpression of microglia marker Iba1 in the hippocampus induced by lipopolysaccharides (LPS) and inhibit the activation of microglia. It probably has a neuroprotective effect by inhibiting the activation of hippocampal microglia and activating the neuronal FGF-2/FGFR1 signal pathway [72]. Although there is no conclusive evidence that PF treats AD by protecting microglia, the treatment of PF plays a key role in the inhibition of the activation of microglia [49].

#### 4.2. Protection of Astrocyte

Astrocytes are a kind of neuroglial cells, which play essential roles in supplying energy to neurons, modulating local blood flow, neural circuit function, synaptic plasticity, and development [73, 74]. This study has shown that neurovascular injury during the onset of AD would cause astrocyte atrophy, which, in turn, promotes the deterioration of AD [75]. Thus, as one of the early features of AD, the reactivity of astrocytes is expected to become an important target for preclinical diagnosis and treatment [76]. PF can activate adenosine A1R and further alleviate astrocyte activation and neuroinflammation in 5XFAD mice to improve the symptoms of AD [31]. Research showed that PF protects astrocytes by participating in the biosynthesis of TSPO and neurosteroids and then plays a therapeutic role in neurodegenerative diseases such as AD [47]. PF can inhibit the release of microglial chemokine CCL2 and CXCL1 stimulated by $\text{A}\beta_{1-42}$, reduce the chemotaxis of microglia, and then treat AD [49].

#### 4.3. Protection of Oligodendrocyte

Neuroimaging studies show that white matter degeneration and demyelination may also be important pathophysiological features of AD, and the formation of myelin is closely related to...
oligodendrocytes [77]. Considerable research implicated that myelin destruction and oligodendrocyte dysfunction may cause reduction of excessive deposition of Aβ through neuroinflammation. Oligodendrocytes may be a new breakthrough in the prevention and treatment of AD [78]. Shenzhiling oral solution can protect oligodendrocytes by downregulating the acetylation level of histone H3 and the level of MBP gene by epigenetic regulation. The protective effect of Shenzhiling oral solution on oligodendrocytes is related to PF [79] (Table 3).

5. Regulation of Neurotransmitters-Related Enzymes and Receptors

5.1. Inhibition of Ca^{2+}-Related Proteases. Calpain is a kind of calcium-dependent cysteine protease, which is mainly divided into three types: calpain1 (u-calpain), calpain2 (m-calpain), and calpain3 (p94). Studies have shown that PF may inhibit u-calpain by reducing the concentration of calcium in SH-SY5Y cells induced by okadaic acid (OA) and eventually reversed tau hyperphosphorylation [40].

5.2. Regulation of Acetylcholine-Related Enzymes. The cholinergic system of the brain is closely related to age-related cognitive decline. Studies indicate that the gradual loss of cholinergic innervation in the margin and neocortex is one of the reasons for the formation of AD. The loss of innervation is closely related to the synthesis and hydrolysis of acetylcholine involved in choline acetyltransferase (ChAT) and acetylcholinesterase (AChE). It has been found that the increase of AChE in the brain of patients with AD can promote the excessive deposition of Aβ, while the decrease of ChAT transport can lead to the aggravation of dementia symptoms [80–83]. PF could decrease the activity of AChE and increase the activity of ChAT in the brain of Aβ1–42-induced AD rats and restore the cholinergic system and innervation to normal [84].

5.3. Activation of Adenosine Receptor. Adenosine is widely distributed in the CNS and plays a neuroprotective role. Most adenosine functions are mediated by receptors, including A1, A2A, A2B, and A3 receptors (A1R, A2AR, A2BR, and A3R). They can control the release of neurotransmitters including glutamate and acetylcholine, which are involved in the learning and cognitive process, and affect these adenosine receptors, which may change the process of AD to some extent. [85–87]. The neuroprotective effect of PF is mediated by the activation of adenosine A1R. It can significantly reduce the load of Aβ plaque in the brain of mice (Table 4).

**Table 2: The mechanism of protection of neurons in the treatment of AD with Paeoniflorin.**

| Included studies | Year | Animal experiment | Disease model | Clinical trial | Possible mechanisms (signaling pathway) |
|------------------|------|-------------------|---------------|----------------|----------------------------------------|
| Kong et al. [31] | 2020 | 5XFAD mice        | A novel transgenic mouse model of AD | —              | Decreased expression of IL-1 β and TNF-α and reduction of neuroinflammation and by activating adenosine A1R. Preventing tau hyperphosphorylation via recovering SOCS2/IRS-1 signaling and decreasing the contents of TNF-α and IL-1β in the hippocampus |
| Sun et al. [41]  | 2017 | Male Sprague–Dawley (SD) rats | A diabetic rat model with cognitive impairment | —              | The cytoprotection mediated by TSPO and neurosteroids biosynthesis |
| Qiu et al. [48]  | 2018 | Rat astrocytes    | A cellular model of neurodegenerative diseases | —              | — |
| Cho et al. [32]  | 2020 | C6 glial cells were treated with PF and Aβ25–35 | An AD cellular model | —              | Inhibiting the NO production of C6 glial cells |
| Liu and Wang [50] | 2017 | Primary microglia of SD rats | An AD cellular model | —              | Inhibiting the secretion of proinflammatory mediators IL-1 β, IL-6, TNF-α, and chemokine CCL2 and CXCL1 |
| Gu et al. [65]   | 2016 | C57BL/6 × DBA/2 mice | A transgenic mouse model of AD | —              | Increasing Bcl-2/Bax ratio, reducing caspase-3 activity, and inhibiting apoptosis |
| Wang [52]        | 2018 | APP/PS1 mice      | A mouse model of AD | —              | Decreasing the content of ROS, increasing the content of GSH and SOD, upregulating the expression of 15-LOX, increasing the content of NPD1, and reducing the formation of PG, TXB2, and LTB4 |
| Cong et al. [66] | 2019 | TBTC-induced hypothalamic neurons from neonatal rats | An AD cellular model | —              | Inhibition of MKK4-JNK signaling pathway, modulation of the Bcl-2/Bax ratio, and downregulation of cleaved-caspase-3 levels |
| Hu et al. [49]   | 2018 | C57BL/6J mice established by intraplantar injection of CFA | An inflammatory model | —              | Inhibition of TNF-α and IL-1β and the activity of NLRP3 inflammasome to relieve the inflammatory reaction |
6. Inhibition/Activation of Related Signal Pathway

6.1. Inhibition of MAPK Pathway. Mitogen-activated protein kinase (MAPK) family is a kind of serine/threonine protein kinase, which is a group of major signal molecules in the process of signal transduction, and its activation is the final step of intracellular phosphorylation cascade. P38 is the most significant member of MAPK family to control inflammatory response [88, 89]. PF showed therapeutic activities and neuroprotective effect against AD through suppression of the p38 MAPK pathway, alleviating bupivacaine-induced neurotoxicity in neural cells [90]. PF is confirmed to improve the cognitive impairment of AD mice by downregulating the expression of p-p38MAPK and reducing caspase-3 activity and inflammatory reaction [65].

6.2. Inhibition of GSK-3β and NF-κB Pathway. NF-κB protein is a homologous/heterodimer formed by p65 and p50, which is related to synaptic plasticity and memory. GSK-3β is a serine/threonine kinase, which is ubiquitous in mammalian eukaryotic cells. It can act on many signal proteins, structural proteins, and transcription factors and regulate cell apoptosis, differentiation, and proliferation. Although the role of PF in the treatment of AD through GSK-3β and NF-κB pathway is not completely clear, current studies have shown that PF is likely to inhibit the activation of GSK-3β and NF-κB pathway [49], which suppressed the production of IL-6, IL-1β, and tumor necrosis factor-alpha (TNF-α) [32]. The relevant mechanism needs to be further verified.

6.3. Activation of PI3K/Akt/mTOR Pathway. This study proves that PI3K is an intracellular phosphatidylinositol kinase composed of p85 and p110. Thus, Akt is a protein serine/threonine kinase that acts on cell survival and apoptosis. The mammalian target of rapamycin (mTOR) is an important regulator of cell growth and proliferation. Shenzhiling oral solution may protect myelin sheath and treat AD by upregulating the expression of PI3K, Akt, and mTOR [79] and increasing their phosphorylation. The protective effect of Shenzhiling oral solution is closely related to PF [91] (Figure 4 and Table 5).

7. Summary and Prospect

PF plays a more and more important role in AD, including regulating protein, anti-inflammation, and antioxidation, protecting glial cells and antiapoptosis, regulating neurotransmitters-related enzymes and receptors, activating or inhibiting related signal pathways, and so on. Although the current research on the mechanism of PF in the treatment of AD is very extensive, the vast majority of them are focused on animal experiments and cell experiments, have a lack of large samples of clinical trials and clinical observation, and have not studied clinical dose-effect relationship. In this regard, researchers need to conduct large-scale, randomized,
controlled, double-blind clinical trials to further demonstrate the conclusions of animal experiments and cell experiments, in order to accurately explore the potential clinical role and mechanism of PF in AD.

In recent years, the research focus on the mechanism of the action of PF on AD ranges from neurons to the type of neuroglial cells such as microglia astrocytes oligodendrocytes. Some studies have made a new interpretation of the mechanism of PF to AD from the perspective of lipid metabolism and epigenetics. The further deepening of the research also indicates that researchers have a deeper understanding of the relationship between PF and AD. PF therapy is expected to become a new method and new idea for the prevention and treatment of AD, which will benefit more AD patients.

However, there is still a huge research space in this field. Whether there is a potential relationship between these mechanisms and mechanisms and whether different mechanisms are different forms of expression of the body will be further breakthroughs in future research.

Data Availability

The data used in the current study are included within this article.

Conflicts of Interest

The authors declare that they have no conflicts of interest.
Authors’ Contributions

Zeyu Meng, Huize Chen, and Chujun Deng contributed equally to this work.

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