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Review paper

Pterostilbene: A natural neuroprotective stilbene with anti-Alzheimer's disease properties

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ABSTRACT

Alzheimer's disease (AD) is the leading cause of dementia, and no effective treatment has been developed for it thus far. Recently, the use of natural compounds in the treatment of neurodegenerative diseases has garnered significant attention owing to their minimal adverse reactions. Accordingly, the potential therapeutic effect of pterostilbene (PTS) on AD has been demonstrated in multiple *in vivo* and *in vitro* experiments. In this study, we systematically reviewed and summarized the results of these studies investigating the use of PTS for treating AD. Analysis of the literature revealed that PTS may play a role in AD treatment through various mechanisms, including anti-oxidative damage, anti-neuroinflammation, anti-apoptosis, cholinesterase activity inhibition, attenuation of β-amyloid deposition, and tau protein hyperphosphorylation. Moreover, PTS interferes with the progression of AD by regulating the activities of peroxisome proliferator-activated receptor alpha (PPAR-α), monoamine oxidase B (MAO-B), silent information regulator sirtuin 1 (SIRT1), and phosphodiesterase 4A (PDE4A). Furthermore, to further elucidate the potential therapeutic mechanisms of PTS in AD, we employed network pharmacology and molecular docking technology to perform molecular docking of related proteins, and the obtained binding energies ranged from −2.83 to −5.14 kJ/mol, indicating that these proteins exhibit good binding ability with PTS. Network pharmacology analysis revealed multiple potential mechanisms of action for PTS in AD. In summary, by systematically collating and summarizing the relevant studies on the role of PTS in treatment of AD, it is anticipated that this will serve as a reference for the precise targeted prevention and treatment of AD, either using PTS or other developed drug interventions.

1. Introduction

Alzheimer's disease (AD) is an age-associated neurodegenerative disease, characterized by cognitive dysfunction and reduced motor behavior ability and adversely affects the quality of life of patients [1]. Individuals with obesity or diabetes are more likely to develop AD in middle and old age compared to other populations, which further exacerbates the difficulty of disease treatment [2]. Statistics indicate that there are more than 46 million patients with AD worldwide, making it a severe social and public health problem. In 2020, the cost of addressing AD in China accounted for 1.47% of the gross national product, far surpassing the world average (1.09%). The total annual cost of addressing AD in China is expected to reach 507.49 billion US dollars in 2030 [3]. The pathological changes in AD mainly manifest as senile plaques (SP), caused by the abnormal deposition of β-amyloid protein (Aβ), and neurofibrillary tangles (NFT), formed by hyperphosphorylation of the microtubule-binding protein tau in brain tissue [4–6]. Additionally, the neuroinflammatory response, oxidative stress injury, mitochondrial dysfunction, abnormal autophagy and apoptosis, synaptic structure changes, and the destruction of the blood-brain barrier (BBB) are all implicated in the occurrence and development of AD [7–9].

For several years, research has been ongoing to develop drugs to prevent and treat AD; however, no substantial progress has been

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made so far [10]. Currently, acetylcholinesterase (AchE) inhibitors and *N*-methyl-D-aspartate (NMDA) receptor antagonists are widely used therapeutic drugs for AD in clinical practice; however, these drugs can only delay AD progression and have strong adverse reactions [11–13]. Multitarget drugs offer superior therapeutic effects, a lower risk of drug interactions, and more predictable pharmacokinetic and pharmacodynamic profiles. Concurrently, multitarget-directed ligands may represent a novel approach to mitigate drug resistance by intervening in two or more AD causative factors, potentially leading to enhanced therapeutic outcomes [14]. The development of multitarget lead compounds from natural products for the treatment of AD has emerged as a significant area of interest in pharmaceutical research [15].

Pterostilbene (PTS) is a naturally occurring compound found in plants such as blueberries (*Vaccinium*) and Chinese dragon's blood, belonging to a class of compounds termed phenylpropyl [16]. Owing to its structural similarity to resveratrol, it is therefore sometimes referred to as an analogue of resveratrol [17]. PTS exhibits a variety of biological activities and potential neuroprotective effects. Qu et al. [18] suggest that PTS has a variety of physiological activities and is expected to become a new drug for the treatment of central nervous system diseases. Additionally, PTS is a powerful antioxidant that can protect cells from oxidative stress by reducing free radical production and clearing the generated free radicals [19]. Moreover, PTS exerts its biological activity by influencing multiple signaling pathways and regulating gene expression [20]. It can regulate the activity of various transcription factors, such as nuclear factor kappa B (NF-κB), activator protein 1 (AP-1), and nuclear factor-E2 p45-related factor 2 (Nrf2), and thus modulate BP such as inflammation, apoptosis, and the cell cycle [21]. PTS can prevent apoptosis through various mechanisms, including regulating the expression of apoptosis-related proteins and modulating signaling in apoptosis-related pathways [22]. PTS can also interact with several transcription factors, affecting their activation or inhibition, thereby regulating gene expression. Consequently, this results in PTS exhibiting a wide range of biological effects, including anti-tumor, anti-aging, and anti-inflammatory efficacy [23–25].

Although various *in vivo* and *in vitro* experiments have demonstrated that PTS plays a therapeutic role in AD and may improve cognitive function in animal models of AD, there is still a lack of clinical evidence supporting its use for AD treatment. Therefore, it is necessary to systematically and extensively explore the pharmacological effects of PTS on AD. Network pharmacology can systematically and efficiently reveal the potential complex interactions between drug active ingredients and disease targets and examine the effects of these interactions on system function and behavior [26]. Here, we reviewed and summarized the results of *in vivo* and *in vitro* studies investigating the use of PTS in AD treatment. Additionally, using network pharmacology, we screened the targets of PTS in AD treatment and performed molecular docking on PTS and its target proteins to further predict and simulate their binding interactions, thereby providing a theoretical basis for further experiments and clinical applications.

2. PTS: a brief overview

PTS was first isolated and identified as an active component in sandalwood heartwood (*Pterocarpus santalinus*) in 1972 [27]. Subsequently, it was identified in *Dracaena cochinchinensis*, blueberries, grapevines, and propolis [28]. PTS, chemically identified as 3,5-dimethoxy-4-hydroxytrans stilbene (Fig. 1), is a white crystalline powder and dimethylated derivative of the phytoalexin resveratrol with a molecular formula of $C_{16}H_{16}O_3$, a molecular weight of 256.3, and a melting point of 89–92 °C [29,30]. Its physiological activity is superior to that of resveratrol, which is classified among the 100

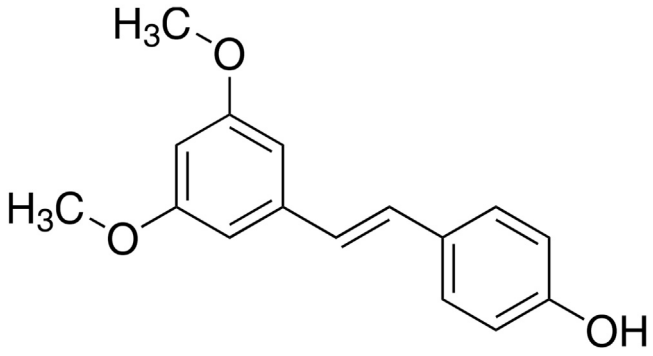

Fig. 1. Chemical structure of pterostilbene (PTS).

most effective anti-aging substances by the American Anti-Aging Bible [31]. In nature, PTS exists in two forms, namely *cis*-PTS and *trans*-PTS. *Trans*-PTS exhibits a wider range of physiological activities than *cis*-PTS and can be converted to *cis*-PTS under long-wavelength ultraviolet light [32].

PTS is found in only a few plants and in relatively low quantities [33,34]. Although several studies have described the presence of PTS in blueberries and grapes, the concentration of PTS in these plants is very low (Table 1) [35–37]. For example, the concentration of PTS ranges from 9.9 to 15.1 mg/kg in blueberries, 0.2–4.7 mg/g in grape skins, and 99–151 mg/kg in dried samples of rabbit-eye blueberry (*Vaccinium ashei*) [37]. Notably, the highest abundances of PTS in nature are found in *Guibourtia tessmannii*, Indian Kino (*Pterocarpus marsupium*), and *Vaccinium* spp. [36].

PTS has potential for a wide range of applications in medicine, health food, and cosmetics because of its pharmacological effects, which include anti-oxidative, anti-aging, neuroprotection, cell proliferation inhibition, anti-cancer, and anti-metabolic disease properties. However, further research and application of PTS and its derivatives is challenging owing to their limited quantity in nature [38–40]. A comparative study of biological activities has revealed that chemically synthesized stilbenoid compounds exhibit the same activity as naturally derived substances [41]. Therefore, exploring the simple and safe total synthesis and structural modification of PTS and its derivatives is one of the prominent research areas for PTS.

The primary methods for obtaining high-purity PTS include: i) Extraction from natural plants: PTS is widely found in Guangxi dragon's blood, propolis, blueberries, and grapevines. Presently, the most common methods primarily involve directly extracting PTS from plants, and studies mainly focus on methods for determining PTS content in plants and pharmacological evaluation of their anti-oxidative, anti-cancer, and neuroprotective effects [42–45]. However, the limited quantity of natural PTS leads to high extraction costs, which is not conducive to the promotion and application of PTS [46]. ii) Genetic and environmental factors influence the availability of PTS in plants [47]. For example, fungal infections induce elevated PTS production in certain crops, such as grapes,

Table 1
Potential dietary sources of pterostilbene (PTS).

Source	Concentration range	Refs.
Fungal infected grapes	0.2–4.7 mg/g of fresh weight	[35]
Vaccinium berries	99–520 ng/g of dry sample	[36]
Blueberries	9.9–15.1 mg/kg of fresh weight	[37]
Deerberries	520 ng/g of dry sample	[37]
Rabbit-eye blueberry	99–151 ng/g of dry sample	[37]

whereas ultraviolet exposure increases resveratrol production while decreasing PTS production in grapevines [48,49]. Transgenic modification of phenolic metabolism is considered as a viable strategy for increasing the production of PTS from dietary sources [50]. Additionally, *Nicotiana tabacum* L. can be transformed to produce PTS by employing a stilbene synthase transgene from peanuts along with an *O*-methyltransferase transgene from *Sorghum* bicolor (L.) Moench [36]. iii) Biosynthesis: the biosynthesis of PTS is still in the preliminary stage of research. Pezet et al. [51] originally investigated the metabolism of resveratrol and the effects of some enzymes *in vivo* following resveratrol synthesis and identified that PTS is synthesized under the action of methylase. However, the specific regulations underlying this process remain unclear. Moreover, the direct conversion of resveratrol into PTS catalyzed by resveratrol-*O*-methyltransferase has been verified in plants, which provides a promising new direction for PTS biosynthesis [52].

3. Progress in the chemical synthesis of PTS

Continual in-depth research on the various biological activities of PTS has attracted increasing attention from experts globally [53]. However, because the quantity of PTS in natural resources is limited and extraction costs are high, it is vital to explore a chemical synthesis route suitable for industrialization and to allow further development and utilization of PTS [54,55]. In the following section, the main synthetic routes of PTS are reviewed based on different synthetic methods (Fig. 2), providing a brief analysis and evaluation of each.

Roberti et al. [56] synthesized PTS via a Wittig reaction using the *tert*-butyl dimethylsilyl (TBDMS) group as a protective group. McLeod et al. [57] employed 3,5-dihydroxybenzoic acid as a raw material; initially, the hydroxyl group was methylated to produce a methoxy group, and then the carboxyl group was reduced using sodium boron hydride. Following this, the 4′-hydroxyl group was protected using tetramethylthiocarbamide, and subsequently, a deprotection reaction was used to obtain PTS. This method also employs a Wittig reaction to synthesize PTS; however, this reaction has poor stereoselectivity, low yield, and produces a large amount of triphenyl phosphorus, which is an environmental pollutant byproduct [58]. Additionally, PTS synthesis via the Wittig reaction has additional challenges that are difficult to overcome. Through advancements in synthesis methods, the Wittig-Horner reaction has replaced the Wittig reaction to become the predominantly used method for constructing trans double bonds [59]. The Wittig-Horner reaction employs milder conditions, is simpler to operate, has higher yields, and the product generated is a single trans structure [60]. A series of PTS glycosides and 3′-methoxy PTS were synthesized through a Wittig-Horner reaction using 3,5-dihydroxybenzoic acid, vanillin, or p-hydroxybenzaldehyde as starting materials and methoxy to protect the hydroxyl group of p-hydroxybenzaldehyde [16]. By protecting the hydroxyl group of p-hydroxybenzaldehyde using a benzyl group, PTS can also be synthesized through a Wittig-Horner reaction by forming double bonds with 3,5-dihydroxybenzoic acid as the raw material [61].

Silvestre-Alcantara et al. [62] used an isobutyl group to protect the hydroxyl group of p-hydroxybenzaldehyde to synthesize PTS and its analogues, achieving a 32% yield for PTS. Lee et al. [63] synthesized a series of PTS derivatives using a benzyl group as the hydroxyl protection group and demonstrated that PTS and its derivatives obtained had superior antioxidant properties to vitamin E. Furthermore, Lion et al. [64] successfully synthesized PTS by using a methyl methoxy group as the protective group for the phenolic hydroxyl group, and demonstrated that PTS and its analogues exhibited pronounced inhibitory effects on tumor cells and cell apoptosis.

The Heck reaction is a coupling reaction between an aryl halide and an alkene or alkylamine catalyzed by palladium [65]. The reaction conditions are mild, with simple operating conditions and high *trans*-stereoselectivity [66]. Guiso et al. [67] demonstrated a

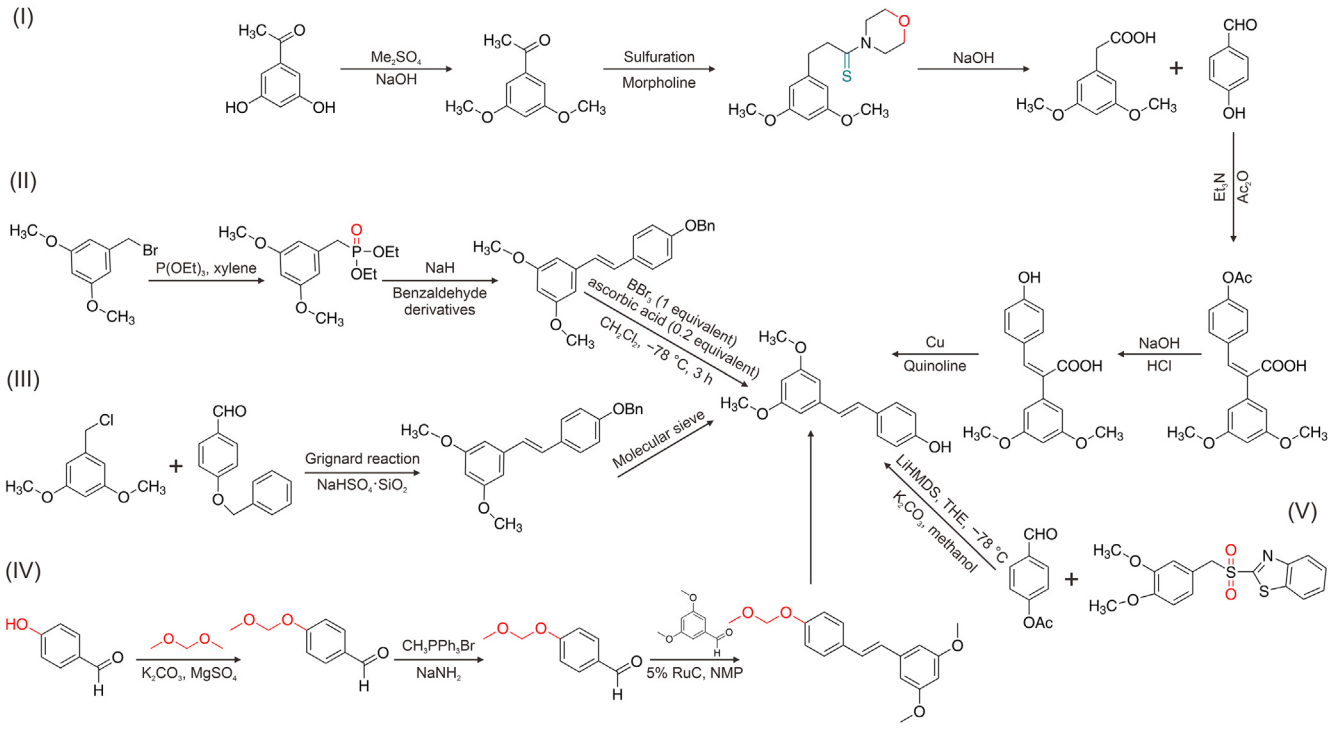

Fig. 2. The chemical synthesis pathways of pterostilbene (PTS). I–V indicate five different pathways to synthesize PTS. LiHMDS: lithium hexamethyldisilazide; THE: tetrahydrofuran RuC: ruthenium carbonyl; NMP: *N*-methyl-2-pyrrolidone.

novel method to synthesize resveratrol. They used the Heck reaction involving acetyl-iodobenzene and 3,5-diacetylstyrene to obtain resveratrol acetyl ester after hydrolysis. Resveratrol was obtained by removing the protective acetyl group. The procedure, although simple, requires the preparation of the intermediate 3,5-diacetoxystyrene via a Wittig reaction. Cai et al. [66] employed 3,5-dimethoxybenzaldehyde as the starting material to synthesize PTS using a similar synthesis route, achieving a total yield of 81%.

In summary, the existing synthesis routes for PTS have their own unique advantages and disadvantages. The widely studied Wittig and Wittig-Horner reactions are simple and mild; however, the challenge of low yield persists owing to the involvement of multiple steps in the synthesis process, which remains to be addressed. Recently, the Heck reaction, with its mild conditions and high selectivity, has attracted increasing attention from researchers; however, the high cost of raw materials and catalysts hinders its application in large-scale industrial production. Therefore, it is crucial that existing processes are optimized and novel processes are explored for the industrialization of PTS as well as for its development and promotion.

4. Pharmacokinetics

In daily life, PTS is ingested by the human body through sources such as grapes, berries, and nuts, among other foods. Mice continuously fed a PTS (3000 mg/kg/day) dose for 28 days did not exhibit any toxic reactions [68]. Dose dependence is one of the characteristics of PTS pharmacokinetics. Intravenous administration of PTS (25 mg/kg) resulted in a nearly two-fold decrease in the clearance rate owing to the saturation of PTS metabolism. Increasing the dose of PTS administered orally from 15 to 30 or 60 mg/kg doubled the bioavailability and prolonged the mean retention time, a trend attributed to the absorption and limited clearance of PTS [69]. In addition, sublingual administration of 2.5 mg/kg of PTS resulted in rapid absorption and moderate bioavailability [70].

4.1. Absorption

Owing to its low polarity surface area, lipophilicity, hydrogen bond acceptor and donor properties, as well as rotatable bonds, PTS exhibits high membrane permeability. PTS exhibits good bioavailability, which may be attributed to the incorporation of two methoxy groups onto the A-phenyl ring of resveratrol [71]. In contrast to resveratrol, PTS is rapidly absorbed. For example, following a single oral dose (PTS 56 mg/kg, resveratrol 50 mg/kg), the peak plasma concentration (c_{max}) value of PTS was 36 times higher than that of resveratrol, and the time to maximum plasma concentration (t_{max}) was twice that of resveratrol. Furthermore, the oral bioavailability of PTS was 66.9%, while that of resveratrol was 29.8% [72]. However, the water solubility of PTS is poor (21 g/mL), thus affecting its absorption. The solubility of piperazine-PTS cocrystals was six times higher than that of PTS, which greatly improved its water solubility [73]. Solubilizing excipients such as 2-hydroxypropyl-cyclodextrin (HP-CD) also improved the bioavailability of PTS; specifically, the bioavailability of HP-CD PTS solution (F = 59.2, 19.6%) was significantly higher than that of PTS suspension (F = 15.9, 7.8%) [70]. In addition, postprandial administration of PTS also increases its absorption, primarily because of increased bile secretion after eating, which in turn improves the water solubility of PTS taken concurrently with food [69]. Combining PTS with a HP-CD (15 mg/kg) solution also increased its bioavailability and total plasma levels of both its metabolites and parent compounds [70].

4.2. Distribution

After intravenous administration in rats, PTS (steady-state volume (V_{ss}) = 5.3 L/kg) exhibits an apparent volume of distribution exceeding total body water (V_{ss} = 0.7 L/kg), indicating substantial tissue distribution [72]. The tissue distribution of PTS in C57 BL/6 mice showed that following the oral administration of PTS (28 mg/kg) for 20 min, the order of tissue distribution was stomach > liver > kidney > intestine > ung > brain > spleen > skeletal muscle > heart. Furthermore, the highest concentration of PTS in the brain tissue was 10.3 ± 3.2 μg/g at 45 min of drug administration, suggesting that PTS easily crosses the BBB [74]. Choo et al. [75] also demonstrated that PTS was distributed in the liver, kidney, heart, lung, and brain tissues. The major metabolites of PTS are sulfate and glucuronide conjugates [72]. After intravenous administration in male rats, the sulfate conjugate was more extensively distributed than the glucuronic acid conjugate, and the gut-hepatic circulation of the metabolites was confirmed, as evident by the increased concentration of glucuronate-acidized PTS 1–2 h after oral administration [76].

4.3. Metabolism

The hepatic cytochrome P450 system plays a key role in drug metabolism by converting drugs from a hydrophobic form to a more readily excretable hydrophilic form. Bioconversion reactions can generally be classified as either cytochrome P450-dependent phase I or II combined reactions. Phase I enzymes are responsible for the bioconversion of compounds to reduce their toxicity and increase their polarity, thereby facilitating the elimination of drugs from the system. Conversely, phase II-mediated enzymes are involved in the bioconversion of the heterologous metabolites of phase I metabolites, thereby preventing the accumulation of phase I intermediates. PTS is primarily cleared through the phase II drug metabolism pathway involving glucuronidation and sulfation [77]. The involvement of this metabolic pathway is evidenced by the increased concentrations of glucuronide and sulfate PTS binders in the systemic circulation compared to the parent compound forms [72]. Glucuronic acid and sulfate metabolites are the major metabolites of PTS in mice [78]. Under similar conditions, as determined using human liver microsomes, 68% of resveratrol was bound to glucuronic acid, and more than 75% of PTS remained unchanged. Therefore, PTS exhibits high metabolic stability and bioavailability in humans [79].

4.4. Excretion

PTS was excreted as glucuronic acid in male Sprague-Dawley (SD) rats, and most of the glucuronic acid-bound metabolites were excreted 12 h after administration. Glucuronic acid-bound PTS metabolites increased at 2 h, indicating their hepato-enteric circulation. These metabolites are cleared by non-renal pathways, with renal excretion and hepatic excretion accounting for approximately 0.219% and 99.78% of the total excretion, respectively [80]. The clearance rate of PTS was significantly lower than that of resveratrol in male rats, suggesting the longer therapeutic effectiveness of PTS [77]. At high doses, PTS exhibited limited elimination capacity, with its metabolic rate decreasing by nearly 50% when the administered PTS dose was increased from 2.5 to 25 mg/kg, which may be attributed to the saturation of PTS metabolism [69].

4.5. Toxicity

No toxic effects were observed even when high doses of PTS were administered in a mouse model. Four groups of mice were treated

with varying doses of PTS (0–3000 mg/kg/day) for four consecutive weeks. These different PTS doses had no effect on the water intake or body weight of the mice [68]. Additionally, *in vivo* administration of PTS demonstrated an inhibitory effect on tumorogenesis and metastasis without exhibiting toxic effects [81]. Riche et al. [82] evaluated PTS toxicity in mice after intravenous administration of 30 mg/kg/day PTS for 23 days and demonstrated no concomitant systemic or organ-related toxicity even at this high dose, suggesting that PTS is safe. In adults with hyperlipidemia, administration of 100–250 mg of PTS daily produced no significant hepatic or renal adverse drug effects and was well tolerated at twice-daily doses [77]. Taken together, data obtained from animal models and human studies indicate that this compound has no significant toxic effects.

5. Pharmacological mechanisms of PTS in AD treatment

Owing to the complexity of the pathophysiological mechanism underlying AD, its histopathological characteristics have become a prominent focus of current research, especially the changes in Aβ and NFT in brain tissue [83]. Both of these pathological mechanisms damage neurons by reducing mitochondrial function and synaptic plasticity through different mechanisms, leading to progressive cognitive, memory, and motor ability decline in patients with AD [84]. The cleaving of amyloid precursor protein (APP) by beta-site APP cleaving enzyme-1 (BACE1), β-secretase, and γ-secretase subsequently leads to an imbalance between the production and hydrolysis of Aβ, causing the aggregation of a large amount of Aβ and the formation of Aβ plaques. This subsequently leads to excessive accumulation of amyloid Aβ in the hippocampal cortical cell area of the brain, eventually leading to neurodegenerative dysfunction and triggering the inflammatory response in the central nervous system [85–87]. Induced by hyperphosphorylation, tubulin tau polymerizes into spiral fibers in neurons to form NFTs, which disrupts the stability of microtubule connections and subsequently blocks protein transport between neurons and synaptic communication [88]. Currently, cell culture and animal experiments indicate that PTS can improve brain metabolism by inducing the attenuation of neuronal inflammation, anti-oxidative stress effects, inhibiting apoptosis, and neuroprotective effects, consequently playing a role in the prevention and treatment of AD (Fig. 3). Therefore, this article reviews the corresponding mechanisms to provide a reference for future clinical research.

5.1. PTS alleviates AD by inhibiting oxidative stress

With increasing age, the ability of the body to remove free radicals decreases to varying extents, leading to an imbalance of redox system homeostasis [89]. Therefore, nerve cells are susceptible to oxidative stress damage, consequently leading to neurodegenerative diseases, including AD [90]. Abnormal elevations of reactive oxygen species (ROS) and neuronal oxidative stress damage are observed during the early pathological stages of AD [91]. Several

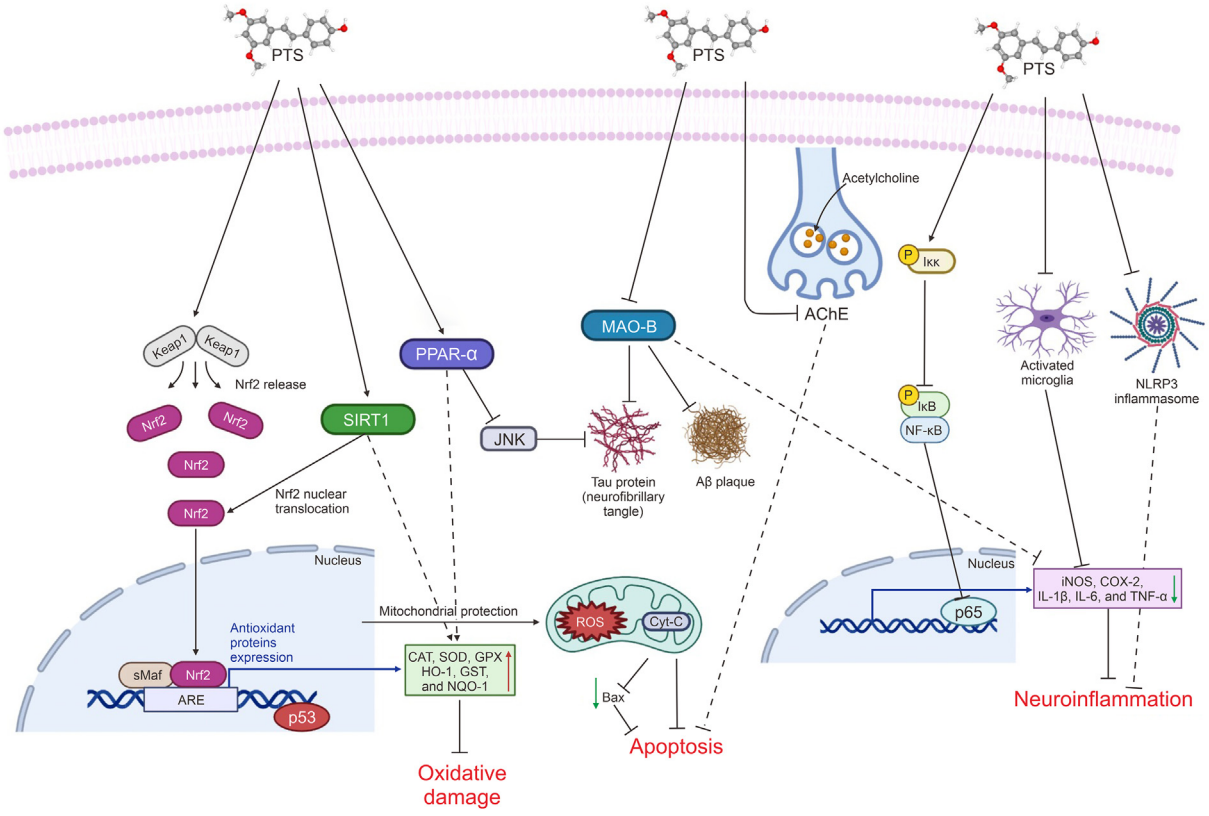

Fig. 3. Panoptic view of the mechanism of action of pterostilbene (PTS). PTS induces the antioxidative response is through the activation and phosphorylation of nuclear factor-E2 p45-related factor 2 (Nrf2) signaling. PTS mediates its anti-inflammatory effect by inhibiting the transcription factors nuclear factor kappa B (NF-κB) and activating protein-1 (AP-1), which leads to the attenuation of downstream pro-inflammatory mediators, including inducible nitric oxide (NO) synthase (iNOS), cyclooxygenase-2 (COX-2), interleukin (IL)-1β, and tumor necrosis factor (TNF)-α. PTS also exerts anti-AD effects by regulating silent information regulator sirtuin 1 (SIRT1), monoamine oxidase B (MAO-B), peroxisome proliferator-activated receptor (PPAR)-α, and acetylcholinesterase (AChE) activities. Keap1: Kelch-like epichlorohydrin (ECH)-associated protein 1; sMaf: small Maf proteins; ARE: antioxidant response element; JNK: c-Jun N-terminal kinase; CAT: catalase; SOD: superoxide dismutase; GPX: Glutathione peroxidase; HO-1: heme oxygenase-1; GST: glutathione *S*-transferase; NQO-1: nicotinamide adenine dinucleotide (phosphate) (NAD(P)H) quinone dehydrogenase 1; ROS: reactive oxygen species; Cyt-C: cytochrome C; NLRP3: NOD-like receptor family pyrin domain containing 3.

factors can lead to oxidative stress damage in AD. Among them, Aβ is a pro-oxidant that contributes to the production of excessive ROS [92]. Nrf2 is a major intracellular regulator that maintains oxidative homeostasis by binding to antioxidant response elements (AREs) under oxidative stress [93]. Moreover, Nrf2 can initiate the transcription of various cytoprotective and antioxidant enzymes/proteins, such as superoxide dismutase (SOD) and heme oxygenase-1 (HO-1) [94]. The anti-oxidative stress effect of PTS is associated with Nrf2 activation. PTS can promote Nrf2 nuclear translocation *in vivo* and *in vitro*, as well as enhance the transcription and expression of antioxidant genes such as HO-1 and SOD. Additionally, PTS nanoemulsion shows stronger antioxidant properties due to improved dissolution and oral bioavailability [95]. PTS also promotes the binding of Kelch-like epichlorohydrin (ECH)-associated protein 1 (Keap1) to p62, thereby enhancing Nrf2 activation [21].

Additionally, aging rats treated with PTS exhibited enhanced cognitive ability in behavioral tests, particularly the Morris water maze and new object recognition tests. This suggested that PTS can improve spatial learning, memory, and object recognition in rats. PTS reduced oxidative stress levels in rat brain tissue and promoted mitochondrial biogenesis, indicating that PTS exerts antioxidant effects and can reduce oxidative damage to cells and oxidative stress in brain tissue [96,97].

5.2. PTS alleviates AD by regulating neuroinflammation

Increasing evidence indicates that abnormal Aβ production and tau protein hyperphosphorylation are directly associated with neuroinflammation [98]. Under physiological conditions, microglia primarily regulate synaptic activity and inflammation by secreting neural cytokines to maintain the normal activity of the central nervous system and the stability of the internal environment [99]. However, when microglia around Aβ plaques are activated, they release substantial amounts of inflammatory mediators, including interleukin (IL)-1β, interferon-γ (IFN-γ), tumor necrosis factor-α (TNF-α), ROS, and nitric oxide (NO) [100]. This causes protein oxidation and induces neuronal inflammation, resulting in neuronal degeneration and damage to the immature BBB [101,102].

PTS inhibited the NOD-like receptor family pyrin domain containing 3 (NLRP3) inflammasome, thereby exerting anti-inflammatory effects [103]. In BV-2 cells with $A\beta_{1-42}$-induced cytotoxicity, PTS inhibited iNOS messenger RNA (mRNA) and protein expression as well as NO production. Additionally, PTS inactivated the NLRP3/caspase-1 inflammasome, which was activated by $A\beta_{1-42}$, decreased the expression and secretion levels of IL-1β, IL-6, and TNF-α, and attenuated $A\beta_{1-42}$-induced cytotoxicity in microglia, indicating that PTS might be an effective therapy for AD by inhibiting over-activated microglia [104].

Toll-like receptor 4 (TLR4) is associated with the immune response and inflammation and plays an important role in recognizing pathogens and inflammatory molecules [105]. NF-κB is an important transcription factor involved in the regulation of inflammatory responses [106]. PTS inhibited the abnormal activation of the TLR4/NF-κB pathway by regulating the composition and functionality of the microbiome. This regulatory effect may be achieved by regulating intestinal permeability, inhibiting the inflammatory response, and reducing oxidative stress [107]. Hou et al. [108] found that PTS treatment alleviated learning and memory impairments caused by lipopolysaccharides (LPS) in mice. Mice administered PTS demonstrated superior learning and memory on behavioral tests. Further exploration of the neuroprotective mechanism of PTS indicated that PTS inhibited the activation level of microglia, protected neurons from damage by inhibiting the inflammatory response of microglia, and alleviated LPS-induced learning and memory impairment.

5.3. PTS alleviates AD by activating peroxisome proliferator-activated receptor alpha (PPAR-α)

PPAR-α is a nuclear receptor that plays a role in regulating lipid metabolism, inflammation, and oxidative stress [109]. Emerging evidence suggests that PPAR-α may be implicated in AD, and several studies have demonstrated its neuroprotective effects [110,111]. PPAR-α activation has been shown to reduce Aβ production, inhibit neuroinflammation, and enhance mitochondrial function, which may contribute to the prevention or mitigation of AD pathology [112,113]. Therefore, targeting PPAR-α using specific agonists or modulators is an emerging area of research interest in AD, as it holds promise as a potential therapeutic strategy.

A PTS diet significantly improved radial arm water maze function in a SAMP8 mouse model of sporadic and age-related AD. Mechanistic studies suggested that PTS activates the endogenous anti-oxidative stress system, up-regulates manganese SOD (MnSOD) expression, decreases phosphorylated c-Jun NH_2-terminal kinase (JNK) levels, and inhibits tau phosphorylation, all of which were ameliorated after PTS administration. This improvement was associated with the activation of PPAR-α activity by PTS. Therefore, PTS may be a potential PPAR-α agonist that exerts anti-AD effects through multiple mechanisms [114].

5.4. PTS alleviates AD by inhibiting monoamine oxidase B (MAO-B)

MAO-B is an enzyme that belongs to the monoamine oxidase family [115]. It is primarily found in the brain and is responsible for catabolizing neurotransmitters such as dopamine, serotonin, and norepinephrine [116]. Furthermore, MAO-B specifically targets and metabolizes monoamines and is involved in regulating their levels in the brain [117]. MAO-B has been implicated in the pathogenesis of AD. Specifically, research has demonstrated that MAO-B levels are elevated in the brains of individuals with AD, particularly in regions affected by the disease, such as the hippocampus and neocortex [118]. Increased MAO-B activity in AD may contribute to the breakdown of neurotransmitters, including dopamine, norepinephrine, and serotonin [119], potentially leading to a decrease in their availability and impaired neuronal communication. Additionally, MAO-B-generated ROS can promote oxidative stress and damage neurons, further exacerbating AD progression [120]. Consequently, owing to their involvement in AD, MAO-B inhibitors have been investigated as a potential therapeutic approach [121,122]. By inhibiting MAO-B activity, these medications aim to preserve and enhance neurotransmitter levels in the brain, potentially improving cognitive function and slowing down disease progression [123].

Li et al. [124] demonstrated that PTS attenuated streptozotocin (STZ)-induced body weight loss and memory impairment by regulating MAO-B. Moreover, administering 20 mg/kg/day of PTS for five weeks significantly improved escape delay and path length in an AD mouse model. Additionally, PTS alleviated $A\beta_{1-42}$ accumulation and tau hyperphosphorylation by downregulating MAO-B expression, inhibited STZ-induced neuronal apoptosis, increased ROS, increased SOD and GSH levels, and exerted anti-oxidative stress effects. Additionally, PTS inhibited the pro-inflammatory cytokines TNF-α, IL-1β, and IL-6 as well as neuroinflammatory responses by inhibiting MAO-B expression. These results indicated that PTS slowed the progression of STZ-induced mouse AD models and demonstrated that PTS is implicated in the inhibition of MAO-B.

5.5. PTS alleviates AD by inhibiting AChE activity

Acetylcholine (ACh) is a neurotransmitter that is essential for normal cognitive and memory function [125]. Typically, ACh levels

are significantly reduced in patients with AD [126]. This is because ACh transmits and regulates signaling between synapses in the brain; however, in AD, the synapses are disrupted and altered, resulting in the decreased release and activity of ACh [127]. Therefore, AChE inhibitors are widely used in AD treatment, as these drugs increase the amount of ACh available by inhibiting AChE activity and prolonging the residence time of ACh within synapses [128]. Through this, they can enhance neurotransmitter transmission and synaptic function and improve cognition and memory in patients. AChE inhibitors, such as donepezil, rivastigmine, and galantamine, are the first-line drugs for AD treatment [129]. These drugs can reduce the symptoms of patients with AD and, in some cases, improve their quality of life. However, AChE inhibitors do not cure AD; they only provide some symptom relief and delay disease progression.

STZ can induce cholinergic dysfunction and increase AChE expression in the brains of rats, inducing AD-like symptoms. PTS significantly decreased the average retention latencies of STZ-induced SD rats in a dose-dependent manner, indicating an improvement in the memory performance of SD rats. Naik et al. [130] demonstrated that PTS inhibited AChE activity, improved cholinergic neurotransmission, and increased ACh availability in the synaptic cleft, thereby ameliorating cognitive impairment in AD rats. PTS also exhibited antioxidant efficacy, increased GSH levels while decreasing MDA levels, and significantly increased the activities of brain ATPases following administration. Moreover, the expressions of TNF-α and IL-6 decreased after PTS administration, suggesting that PTS has antioxidant and anti-inflammatory activities. Other studies have confirmed that a series of PTS compounds (PTS-*O*-acetamidoalkylbenzylamine derivatives and PTS β-amino alcohol derivatives) also inhibited AChE and butyrylcholinesterase (BuChE) and demonstrated that PTS can inhibit the aggregation of $A\beta_{1-42}$ and $A\beta_{1-40}$ induced by human AChE [131,132].

5.6. PTS alleviates AD by activating silent information regulator sirtuin 1 (SIRT1)

SIRTs are a highly conserved family of proteins that function as deacetylases and adenosine diphosphate (ADP)-ribosyltransferases [133]. Their histone deacetylase activity is regulated by nicotinamide adenine dinucleotide (NAD) [134]. Human SIRTs are encoded by SIRT1-7 genes, among which *SIRT1* is the most extensively studied. SIRT1 is involved in the regulation of various physiological (such as apoptosis, autophagy, and aging) and pathological processes (such as diabetes, cancer, and neurodegenerative diseases) [135,136]. Recently, both *in vivo* and *in vitro* AD model experiments have demonstrated that activating SIRT1 can protect nerves through anti-inflammatory and anti-apoptosis effects as well as by reducing amyloid protein accumulation [137–139]. Therefore, SIRT1 may be a potential target for the development of new drugs for AD.

Activation of SIRT1 by PTS further improved neuronal plasticity and delayed neuronal loss, and PTS upregulated Nrf2 expression, increased SOD levels, and inhibited the $A\beta_{25-35}$-induced mitochondrial pathway of apoptosis. Following the administration of the SIRT1 inhibitor EX527, the mitochondrial membrane potential level decreased and the anti-$A\beta_{25-35}$-induced injury of the isolated mouse neurons was attenuated. These results suggested that PTS improves learning and memory ability as well as neuroplasticity in AD rats, potentially by inhibiting the mitochondrial pathway of apoptosis through SIRT1/Nrf2-regulated antioxidant effects [140].

5.7. PTS alleviates AD by inhibiting apoptosis

Apoptosis is a physiological regulatory mechanism involved in the regulation of embryonic development, cell differentiation, and normal cell renewal *in vivo* [141]. However, abnormal cell apoptosis due to interference by pathological factors leads to a variety of diseases. Neuronal loss in the cortex and hippocampus is the main pathological feature of AD [142]. The mechanisms underlying neuronal apoptosis are as follows: i) activation of caspase; ii) $A\beta_{40/42}$ can downregulation of the anti-apoptotic protein B cell lymphoma-2 (Bcl-2) and upregulation of the pro-apoptotic protein Bax expression; ii) induction of Fas/FasL mRNA and caspase-3 and caspase-8 gene expression; and iv) impairment of neuronal survival due to interference of signaling pathways, such as insulin-like growth factor-1 (IGF-1) and insulin signaling pathway, phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt) signaling pathway, extracellular signal-regulated kinase 1/2 signaling (ERK1 and ERK2), protein kinase C (PKC), and calcium pathway [143,144].

In PC12 cells induced by $A\beta_{25-35}$, PTS increased the viability of PC12 cells and decreased the level of apoptosis and intracellular ROS activity. The anti-apoptosis mechanism may be related to the activation of the PI3K/Akt signaling pathway by PTS, which promotes Akt phosphorylation on Ser-473. However, the downstream targets of the anti-apoptosis effects of PTS warrant further investigation [145].

5.8. PTS alleviates AD by targeting phosphodiesterase 4A (PDE4A)

PDE4A is an enzyme belonging to the phosphodiesterase (PDE) family [146]. It plays a role in regulating the intracellular levels of the cyclic adenosine monophosphate (cAMP) signaling molecule [147]. Recently, the dysregulation of cyclic nucleotide signaling, including the cAMP pathway, has been implicated in the pathogenesis of AD. PDE4, including the PDE4A isoform, may contribute to the progression of AD through its modulation of cAMP signaling. PDE4A can degrade cAMP, potentially affecting various cellular processes, including synaptic plasticity, neuronal survival, and inflammation [148]. Inhibiting PDE4A has demonstrated potential therapeutic effects in preclinical studies of AD [149]. Selectively inhibiting PDE4A can increase cAMP levels, which may enhance synaptic function, improve memory, and reduce neuroinflammation associated with Alzheimer's pathology.

PTS-preventive treated APP/PS1 mice exhibited a notable improvement in learning and memory behaviors. PTS can inhibit PDE4A activity and increase cAMP levels. Through this mechanism, PTS can activate cAMP response element binding protein (CREB), which in turn promotes the expression of brain-derived neurotrophic factor (BDNF). *In vitro* experiments confirmed that PTS treatment can reduce Aβ-induced neurotoxicity, neuronal injury, and apoptosis and simultaneously increase synaptic plasticity and neuronal protection (Table 2) [95,96,98,104,107,108,114,124,130,140,145,150]. Therefore, PTS could serve as a potential natural therapeutic for alleviating Aβ-induced AD neurotoxicity by targeting PDE4A [150].

6. Identifying potential targets involved in the protective effects of PTS against AD

To further explore the anti-AD mechanism of PTS, we screened the targets of PTS in AD using network pharmacology. First, we employed SwissTargetPrediction (http://www.swisstargetprediction.ch/) to obtain a PTS database retrieval comprising all possible targets and subsequently used the GeneCards database (https://www.genecards.org/) to screen genes associated with AD (score > 1). The results revealed 100 possible action targets for PTS and 3397 AD-related targets, including 58 intersecting targets; Fig. 4A). The obtained targets (PTGS1, PTGS2, NQO2, ESR1, AHR, RELA, CYP19A1, ABCB1, CA2, APP, PIK3CA, CYP3A4, MAO-A, CYP1A2, SLC6A2, PIK3CB, EGFR, LCK, MAPT,

Table 2
Effects of pterostilbene (PTS) on different neuroprotective mechanisms involved in Alzheimer's disease (AD).

Study types	Cell line(s)/animal model(s)	Experimental dose (*in vivo*/*in vitro*)	Effect	Mechanism	Refs.
In vivo/in vitro	$A\beta_{1-42}$ induced Swiss-Kunming mice/$A\beta_{1-42}$ stimulated SH-SY5Y cell	10, 20, and 40 mg/kg (7 days), i.c.v./1, 3, and 10 μM, 24 h	Reduce ROS content, inhibit the MDA production, reduce the protein levels of Keap1, promote Nrf2 translocation into the nucleus, and increase in HO-1 protein content and SOD activity	Anti-oxidative stress	[98]
In vivo	Aged SD rats	22.5 mg/kg/day, 20 days, i.g.	Increase levels of REST, PSD-95 and mitochondrial porin 1 and promote CREB phosphorylation	Anti-oxidative stress	[96]
In vivo	$A\beta_{1-42}$ induced male C57BL/6 mice	10 mg/kg/day, 20 days, i.g.	Activates the Nrf2 antioxidant signaling, increase in HO-1, SOD content and GSH activity, and inhibit the MDA and H_2O_2 production	Anti-oxidative stress	[95]
In vitro	$A\beta_{1-42}$ induced BV-2 cells	0, 1, 5, 10, and 20 μM, 24 h	Inhibit LDH release, attenuate protein levels of iNOS and NO production, reduce the production of IL-6, IL-1β, and TNF-α, and inhibit NLRP3/caspase-1 inflammasome	Anti-neuroinflammation	[104]
In vivo	High-fat diet plus STZ induced C57BL/6 mice	20 and 60 mg/kg/day, 10 weeks, i.g.	Increase ACh and SOD content, reduce ROS content, inhibit the MDA production, reduce the expression of GFAP and Ib-α, reduce level of LPS, and downregulate the expression of TLR4 and p65NF-κB	Anti-neuroinflammation	[107]
In vivo	LPS induced C57BL/6 mice	20 and 40 mg/kg/day, 7 days, i.g.	Inhibit microglia activation and decrease of LPS-induced production of NO, TNF-α, and IL-6	Anti-neuroinflammation	[108]
In vivo	SAMP8 mouse	120 mg/kg/day, 8 weeks, i.g.	Increase MnSOD expression, rescue PPAR-α expression, decrease levels of phosphorylated JNK, and reduce phosphorylation of tau	Activation of PPAR-α	[114]
In vivo	STZ induced C57BL/6J mice	20 mg/kg/day, 5 weeks, i.g.	Decrease MAO-B expression, attenuate $A\beta_{1-42}$ accumulation and Tau hyperphosphorylation, reduce ROS and MDA levels, increase SOD and GSH levels, weaken the elevation of TNF-α, IL-1β, IL-6, and p-NF-κB, decrease the active caspase-3 and Bax, and increase Bcl-2 expression	Inhibition of MAO-B	[124]
In vivo	STZ induced SD rats	10, 30, and 50 mg/kg/day, 13 days, i.g.	Reduce ROS and MDA levels, increase SOD, CAT and GSH levels, decrease AChE activity, improve ATPases activities, decrease expression of TNF-α and IL-6, and increase in expression of PPAR-α and PGC1-α	Inhibition of AChE activity	[130]
In vivo/in vitro	$A\beta_{25-35}$ induced Kunming mice/$A\beta_{2-35}$ stimulated neurons	10 and 40 mg/kg/day, 5 days, i.g./0.5, 2, and 10 μM, 24 h	Increase the protein SIRT1 and Nrf2, increase neuronal proteins NeuN, PSD-95, and SYN-1, decrease Bax, and increase Bcl-2/Bax	Activation of SIRT1	[140]
In vitro	$A\beta_{25-35}$ induced PC12 cells	5, 10, and 25 μM, 24 h	Increase the cell viability, decrease the apoptosis rate, and inhibit the accumulation of ROS	Anti-apoptosis	[145]
In vivo/in vitro	APP/PS1 mice/$A\beta_{25-35}$ stimulated neurons	5, 10, and 20 mg/kg/day, 13 days, i.g./10 and 20 μM, 24 h	Rescue the reducing in dendritic spine density, increase the cAMP level, and increase the pVASP, pCREB, BDNF, and PSD-95 expression	Regulating PDE4A	[150]

i.c.v.: intracerebroventricular injection; ROS: reactive oxygen species; MDA: malondialdehyde; Keap1: Kelch-like epichlorohydrin (ECH)-associated protein 1; Nrf2: nuclear factor-E2 p45-related factor 2; HO-1: heme oxygenase-1; SOD: superoxide dismutase; SD: Sprague-Dawley; i.g.: intragastric intubation; REST: RE1-silencing transcription factor; PSD-95: postsynaptic density protein 95; CREB: cyclic adenosine monophosphate (cAMP) response element binding protein; GSH: glutathione; LDH: lactate dehydrogenase; iNOS: inducible nitric oxide (NO) synthase; IL: interleukin; TNF: tumor necrosis factor; NLRP3: NOD-like receptor family pyrin domain containing 3; STZ: streptozotocin; Ach: acetylcholine; GFAP: glial fibrillary acidic protein; Ib-α: ibuprofen-alpha; LPS: lipopolysaccharide; TLR4: Toll-like receptor 4; NF-κB: nuclear factor kappa B; MnSOD: manganese SOD; PPAR: peroxisome proliferator-activated receptor; JNK: c-Jun NH_2-terminal kinase; MAO-B: monoamine oxidase B; NF-κB: nuclear factor kappa B; Bcl-2: B cell lymphoma-2; CAT: catalase; AChE: acetylcholinesterase; PGC1: PPAR-γ coactivator 1; SIRT1: silent information regulator sirtuin 1; NeuN: neuronal nuclear protein; SYN-1: synapsin-1; APP: amyloid precursor protein; PS1: presenilin 1; VASP: vasodilator-stimulated phosphoprotein; BDNF: brain-derived neurotrophic factor; PDE4A: phosphodiesterase 4A.

CYP2C9, CYP2C19, SYK, HMGCR, ALOX5, DYRK1A, MIF, ELANE, HSD11B1, CHEK1, WEE1, HDAC3, HDAC1, BRD4, RAF1, MAPK8, MAPK14, MAPK10, CSNK1D, PRKACB, MAP2K2, PRKACA, MAPK9, FRK, CSNK1E, DDR1, CIT, STK32B, JAK2, CYP17A1, MMP3, MCL1, Bcl-2, HDAC6, MTOR, MAPK1, HTT, ABL1, and EPHX2) were imported into Cytoscape 3.9 software to construct a drug target-disease network, and the Search Tool for the Retrieval of Interacting Genes/Proteins (STRING) database (https://cn.string-db.org/) was used to complete a protein-protein interaction (PPI) network. We also performed Gene Ontology (GO) (top 10) and Kyoto Encyclopedia of Genes and Genomes (KEGG) (top 10) analyses on the "drug-disease" targets of PTS and AD through network pharmacology analysis. GO enrichment analysis is based on three main categories: biological process (BP), cellular component (CC), and molecular function (MF). These encompass peptidyl-serine phosphorylation, peptidyl-serine modification, response to oxidative stress, and protein serine/threonine kinase activity, among others. KEGG enrichment analysis identified 79 signaling pathways, and the top 10 key signaling pathways are presented in a bubble diagram (Fig. 4B). These include endocrine resistance, prolactin signaling pathway, chemical carcinogenesis-receptor activation, and the Fc epsilon receptor I (RI) signaling pathway. This also confirmed the possible biological pathways of PTS in the treatment of AD, suggesting that PTS has the potential to be developed as a promising drug.

Hub genes were screened in the interaction network using the Cytoscape plugin Cytohubba. The Matthews correlation coefficient algorithm was used to screen out the top five hub genes in the

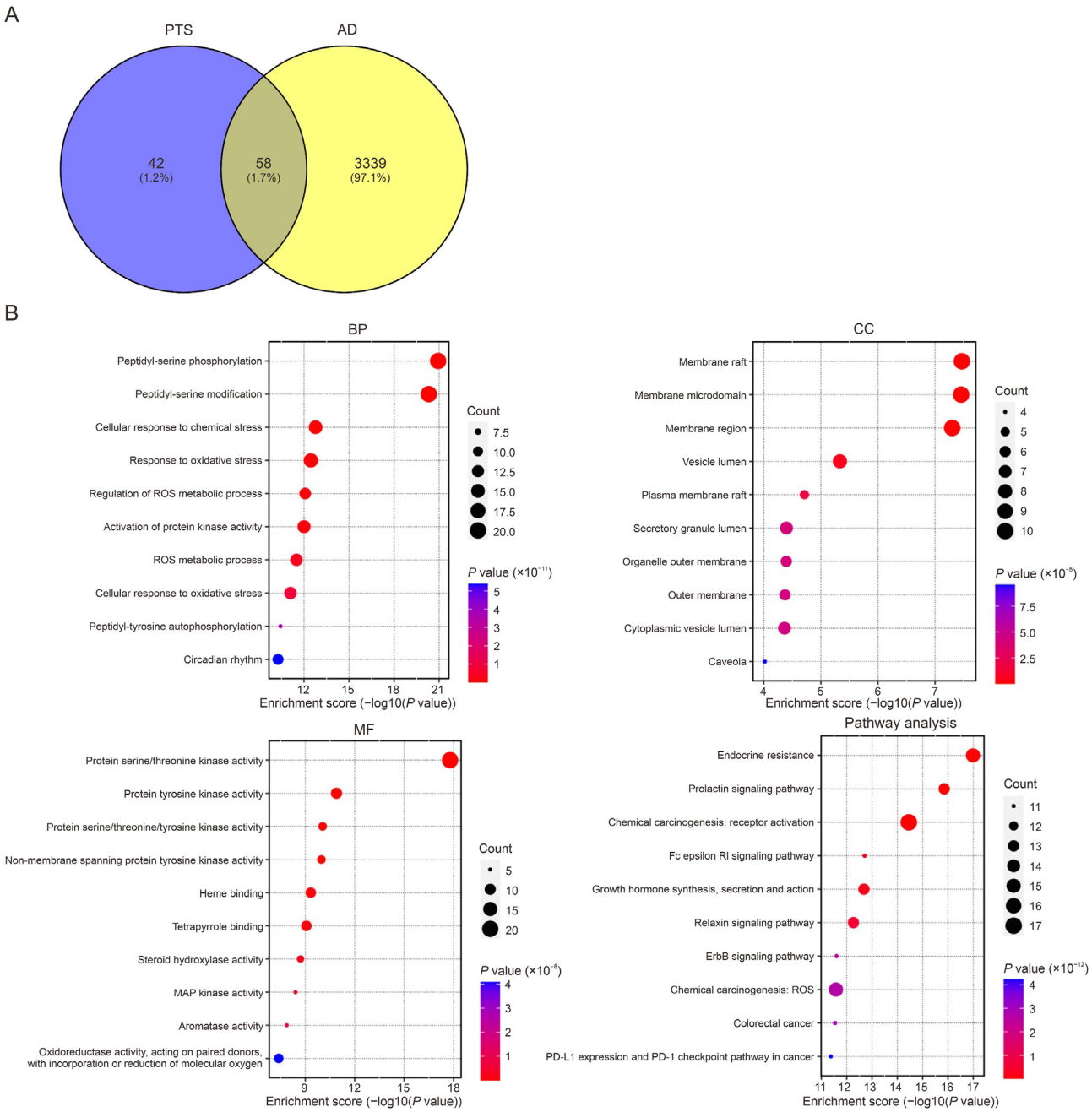

Fig. 4. "Drug-disease" targets of pterostilbene (PTS) in Alzheimer's disease (AD): Gene Ontology (GO) (top 10) and Kyoto Encyclopedia of Genes and Genomes (KEGG) (top 10) enrichment analyses of common targets. (A) The 58 intersecting targets of PTS in AD. (B) GO enrichment analysis includes biological processes (BP), cellular components (CC), molecular functions (MF), and pathway analysis. ROS: reactive oxygen species; MAP: mitogen-activated protein; RI: receptor I; ErbB: erythroblastic leukemia viral oncogene homolog; PD-L1: programmed death-ligand 1; PD-1: programmed cell death protein 1.

target proteins, and a hub gene network map was constructed. Based on this, we suggest that Bcl-2, EGFR, ESR1, MTOR, and RELA are key targets for PTS intervention in AD (Fig. 5A). The binding energy of these hub genes was −5.14, −4.22, −2.83, −3.54, and −3.45 kcal/mol, respectively, indicating a good docking effect. Finally, we verified the reliability of the targets obtained through network pharmacology by molecular docking using AutoDockTools 1.5 and PyMOL software combined with the Protein Data Bank (PDB) database (https://www.ebi.ac.uk/pdbe/), focusing on the hub genes described above (Figs. 5B and C).

Bcl-2 is an anti-apoptotic factor that interacts with beclin 1 (BECN1) to modulate autophagy [151]. Studies have demonstrated upregulation of Bcl-2 in the prefrontal cortex of patients with AD, and a negative correlation between Bcl-2 protein expression and immediate recall [152]. Rohn et al. [153] reported that in AD model mice with overexpressed Bcl-2 protein, the processing of APP and the extracellular deposition of Aβ were reduced. *In vitro*, overexpression of Bcl-2 protected neuronal cells from Aβ-induced death. Additionally, the overexpression of Bcl-2 also affected the processing of tau protein, resulting in a reduction in the number of NFTs.

EGFR is a cell surface growth factor receptor that regulates cell proliferation, differentiation, and survival [154]. Studies have shown that EGFR and its mediated related signaling pathways are

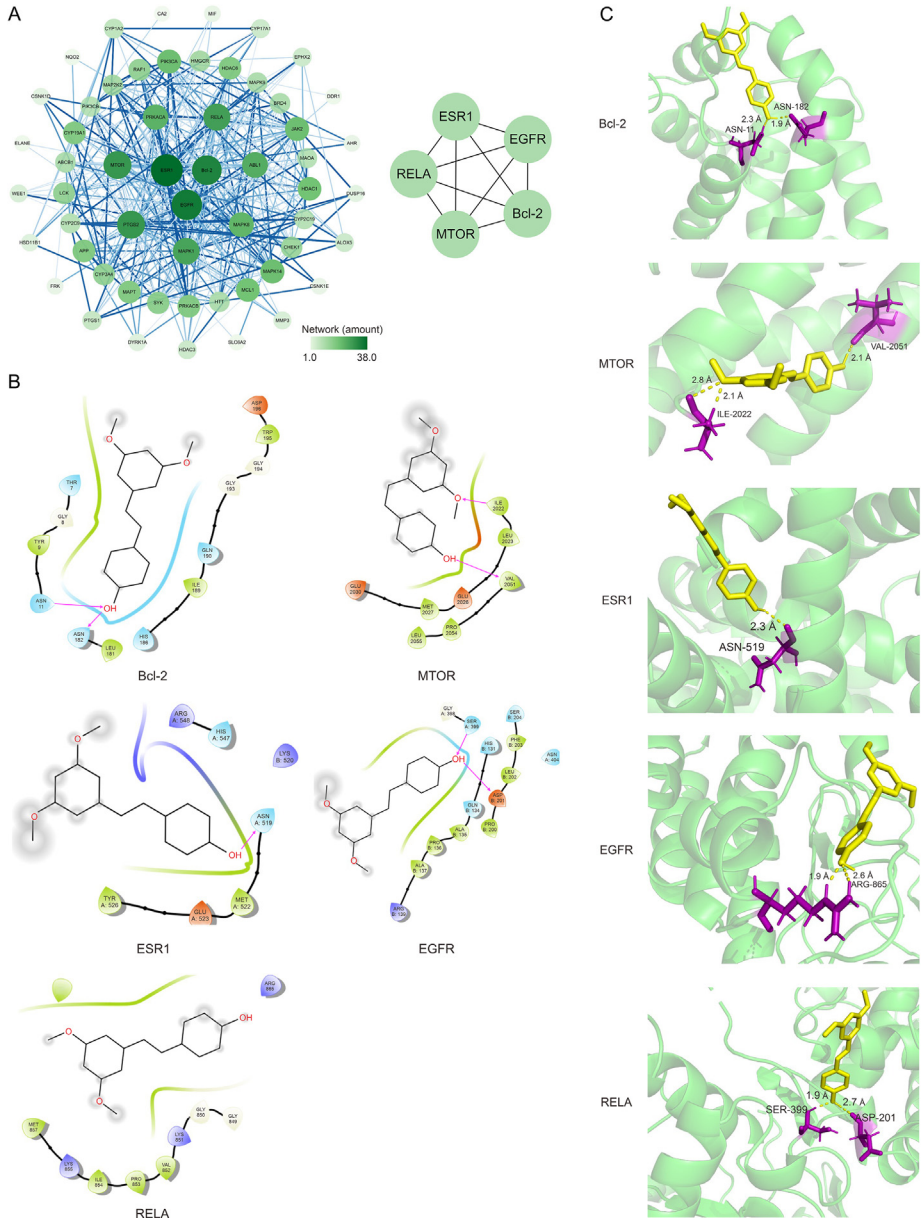

Fig. 5. Potential targets and molecular docking of pterostilbene (PTS) against Alzheimer's disease (AD). (A) A drug-targets-disease network of PTS action targets and AD-related genes. In total, 100 PTS action targets and 3397 AD-related genes were identified, 58 of which are intersecting targets. Hub genes were obtained from the protein-protein interaction (PPI) network, and molecular docking was performed on B cell lymphoma-2 (Bcl-2), EGFR, ESR1, MTOR, and RELA. (B, C) Molecular models of the binding of PTS with Bcl-2, EGFR, ESR1, MTOR, and RELA: the results shown as 2D (B) and 3D (C) diagrams.

key targets in regulating the pathology of AD. For instance, AD patients exhibit high expression of EGFR in the cerebral cortex and hippocampus, which is associated with the formation of neuroinflammatory plaques [155]. The co-expression of EGFR and $A\beta_{42}$ has been shown to synergistically promote memory loss, indicating that EGFR is upregulated in AD [156]. It is noteworthy that recent evidence has demonstrated that the upregulation of EGFR can induce the neurotoxicity and neuroinflammation of $A\beta_{42}$ and activate astrocytes [157]. Compared to wild-type mice, the activation of EGFR in eight-month-old APP/PS1 mice is significantly increased [158]. In *Drosophila* with overexpression of Aβ, excessive expression of EGFR leads to memory impairment [159]. Therefore, targeted inhibition of EGFR may modulate the accumulation of Aβ plaques, neuroinflammation, and cognitive function.

ESR1 plays a central role in the hormonally regulated pathology of AD. In AD, ESR1 mitigates neuronal pathological changes associated with the disease through various mechanisms [160]. The enhancing effects of estrogens on cognitive function diminish with age, and the estrogen deficiency in postmenopausal women may be closely related to AD [161]. Experimental studies have demonstrated that hormone replacement therapy offers protective effects against AD [162]. Estrogen acts as a neuroprotectant, preventing glutamate toxicity, reducing the levels of Aβ, maintaining neurotrophic factors, enhancing synaptic plasticity, alleviating brain inflammation, aiding in the activation of transcription factors, and reducing the hyperphosphorylation of tau protein [163]. Correspondingly, the functions of estrogen are primarily regulated by ESR1 [164]. Therefore, targeting ESR1 may exert anti-AD effects by modulating estrogen levels.

Dysregulation of MTOR is associated with many diseases, such as aging, obesity, diabetes, cardiovascular diseases, and neurodegenerative disorders [165]. MTOR activation serves as a

trigger for the progression of AD and is intertwined with the pathology and clinical manifestations of AD. Signaling pathways involving MTOR are closely related to the formation of Aβ plaques and NFTs [166]. For instance, the activation of MTOR leads to failed clearance of Aβ [167]; MTOR activation accelerates the extent of tau hyperphosphorylation and promotes the onset of AD by impairing the insulin signaling pathway [168]. Therefore, the development of MTOR inhibitors may also contribute to the prevention and treatment of AD [169].

RELA (NF-κB p65), as a key member of the NF-κB family, forms a p65/p50 complex with NF-κB1 (NF-κB p50) to regulate the inflammatory response in the nervous system [170]. Under conditions of oxidative stress, RELA and NF-κB1 are activated, promoting the production of downstream inflammatory mediators, which lead to neuronal apoptosis induced by Aβ, exacerbating the clinical symptoms of AD patients [171,172]. Therefore, targeted inhibition of RELA activation may exert anti-AD effects by suppressing inflammatory pathways and the release of inflammatory factors [173].

7. Enhancement of PTS bioavailability

PTS is insoluble in water, limiting its concentration in the aqueous environment [16]. Using safe PTS preparations with high bioavailability helps to increase bioavailability *in vivo* and subsequently reduces known and unknown side effects [174]. Because of the unique solubility and dissolution rate of drugs, crystal engineering has emerged as a promising approach to improving bioavailability [175]. Cocrystalline formulations can improve the dissolution and bioavailability of PTS and enhance its efficacy. Picolinic acid is an endogenous L-tryptophan metabolite with neuroprotective, immunologic, and antiproliferative properties. Oral administration of PTS-picolinic acid cocrystals in rats led to a 10-fold increase in PTS bioavailability compared with the oral administration of the solid form [16]. Similarly, PTS-caffeine cocrystal solubility was also observed to be more than 27-fold greater than that of the solid form [175].

Poly(3-acrylamide phenylboronic acid-β-PTS) is a round PTS nanoparticle with a particle size ranging from 150 to 250 nm. Notably, they demonstrated a suitable pH and sensitivity to glucose. *In vitro* and *in vivo* studies have demonstrated that PTS nanoparticles are nontoxic and safe. Following administration, these nanoparticles were observed to reduce glucose levels in mice, reverse microinflammation, and improve antioxidant properties [176]. PTS compositions using zein/fucoidan sulfate composite nanoparticles as carriers were prepared via antisolvent precipitation. The findings indicate that this method demonstrates better controlled release and can be used as a potential carrier for the protective encapsulation of PTS [177]. The dissolution of PTS in 2-hydroxypropyl-β-cyclodextrin (HP-b-CD) increased its bioavailability by 3.7 fold [70]. In addition, lipid-based encapsulation systems have been used to enhance the stability of PTS in the aqueous phase. Specifically, Sun et al. [178] investigated the encapsulation of nanoemulsions made from flaxseed oil and olive oil and showed the transportation of a substantial quantity of intact PTS into the intestinal enterocytes via the olive oil nanoemulsion.

8. Future perspectives

AD is a progressive neurodegenerative disorder that is marked by cognitive impairment, behavioral anomalies, and a decline in functional abilities essential for daily living. To date, therapeutic approaches for AD have primarily focused on alleviating symptoms and enhancing quality of life, without effectively halting or reversing the disease's underlying pathology. However, advancements in the understanding of AD's pathological mechanisms have led to the identification of numerous novel therapeutic targets, which hold the promise of novel treatment strategies for AD. In this study, we systematically reviewed and summarized *in vitro* and *in vivo* studies on the treatment of AD with PTS. Literature analysis revealed that PTS may exert therapeutic effects in AD through various mechanisms, including antioxidant damage, anti-neuroinflammation, anti-apoptosis, inhibition of cholinesterase activity, suppression of Aβ protein deposition, and inhibition of hyperphosphorylation of tau protein. Using network pharmacology, we predicted potential therapeutic targets for AD treatment by PTS. The results suggest that Bcl-2, EGFR, ESR1, MTOR, and RELA are key targets for PTS intervention in AD.

Aβ protein aggregation is a key pathological hallmark of AD, with its abnormal deposition resulting in the formation of amyloid plaques that adversely affect the structure and function of neuronal cells. Strategies to target Aβ involve inhibiting its synthesis, enhancing its degradation, and preventing its aggregation. For example, upregulated Bcl-2 protein has been observed to reduce the processing of APP and the extracellular deposition of Aβ, making it a potential therapeutic target for AD treatment. Additionally, targeted inhibition of EGFR may modulate the accumulation of Aβ plaques, neuroinflammation, and cognitive function. Tau protein serves as a stabilizer of microtubules, and its abnormal phosphorylation and aggregation lead to the formation of NFTs, which result in damage to neuronal morphology and function. Inhibiting the phosphorylation of tau and promoting its degradation have emerged as novel strategies for the treatment of AD. Several studies have suggested that inhibiting MTOR activity can reduce tau hyperphosphorylation and delay the progression of AD in animal models. Therefore, targeting MTOR with pharmacological inhibitors or other strategies is a potential therapeutic approach for AD. A growing body of evidence suggests that neuroinflammation plays a crucial role in the pathogenesis of AD. Inhibition of the inflammatory response and regulation of immune balance may offer novel avenues for the treatment of AD. As previous studies have indicated, targeted inhibition of RELA (NF-κB p65) activation may exert anti-AD effects by suppressing inflammatory pathways and the release of inflammatory factors. The identification of these novel therapeutic targets has enriched the research content and direction for AD treatment studies. However, the efficacy and safety of PTS in modulating these targets still require validation through additional clinical trials.

Based on the above overview, we believe that further research on PTS in the future should focus on the following aspects. First, a more comprehensive exploration of the mechanism of PTS in AD is needed beyond simply exploring its anti-inflammatory, anti-apoptotic, anti-oxidative, and neuroprotective effects and should be combined with the deeper pathogenic mechanism of AD to pinpoint the targets of PTS. Network pharmacology analysis of the "drug-disease" targets of PTS in AD provides insights for further exploration of the neuroprotective mechanism of PTS. Second, although the protective effect of PTS on nerve cells has been confirmed through experiments, whether PTS can effectively pass through the BBB requires further investigation. Joseph et al. [97] suggested that PTS can be detected in the serum and brain tissue when administered in large doses; however, when low doses were administered, it was only detected in the serum and not the brain tissue. Therefore, further PTS dosage studies are required to better understand its threshold dose for crossing the BBB. Third, clinical trials have been largely limited owing to the lower-than-expected bioavailability of PTS. To overcome this limitation, various strategies have been explored, including modifying the route of administration and formulating PTS using cocrystals, lipid encapsulants, nanoparticles, and microspheres. Furthermore, the potential

impact of the interaction of many drugs with PTS is unknown. The mode of administration of PTS appears to significantly impact its bioavailability, as the distribution of intravenous doses is higher than that of oral doses. Therefore, prior to the clinical adoption of this promising natural compound, careful consideration needs to be given to the effects of dose, potential drug interactions, and route of administration on drug application.

9. Conclusion

In conclusion, an increasing number of *in vitro* and *in vivo* studies have demonstrated that PTS has the potential to treat AD. PTS may play an anti-AD role through mechanisms including anti-oxidative damage, anti-neuroinflammation, anti-apoptosis, cholinesterase activity inhibition, and reducing Aβ deposition and tau hyperphosphorylation. In addition, we believe that a review of PTS through network pharmacology will provide new avenues for understanding and characterizing the potential of this plant-derived active compound for the treatment of AD. However, the current study still has limitations owing to experimental challenges. Considering the coexistence of the developmental potential of PTS and its associated research challenges, we believe that there is an urgent need for developing PTS as an anti-AD drug. The transition from current PTS research to its future application requires more systematic exploration, and we anticipate that PTS will soon become a widely used clinical drug for AD treatment.

CRediT authorship contribution statement

Songlan Gao: Writing – original draft, Methodology, Data curation, Conceptualization. **Honglei Zhang:** Methodology, Data curation. **Na Li:** Methodology, Data curation. **Lijuan Zhang:** Data curation. **Zhe Zhu:** Methodology, Data curation. **Changlu Xu:** Writing – review & editing, Validation, Supervision.

Declaration of competing interest

The authors declare that there are no conflicts of interest.

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