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Polyphenol-based polymer nanoparticles for inhibiting amyloid protein aggregation: recent advances and perspectives

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Polyphenols are a group of naturally occurring compounds that possess a range of biological properties capable of potentially mitigating or preventing the progression of age-related cognitive decline and Alzheimer's disease (AD). AD is a chronic neurodegenerative disease known as one of the fast-growing diseases, especially in the elderly population. Moreover, as the primary etiology of dementia, it poses challenges for both familial and societal structures, while also imposing a significant economic strain. There is currently no pharmacological intervention that has demonstrated efficacy in treating AD. While polyphenols have exhibited potential in inhibiting the pathological hallmarks of AD, their limited bioavailability poses a significant challenge in their therapeutic application. Furthermore, in order to address the therapeutic constraints, several polymer nanoparticles are being explored as improved therapeutic delivery systems to optimize the pharmacokinetic characteristics of polyphenols. Polymer nanoparticles have demonstrated advantageous characteristics in facilitating the delivery of polyphenols across the blood-brain barrier, resulting in their efficient distribution within the brain. This review focuses on amyloid-related diseases and the role of polyphenols in them, in addition to discussing the anti-amyloid effects and applications of polyphenol-based polymer nanoparticles.

KEYWORDS

amyloidogenic property, polyphenols, nanoparticles, brain targeting, nanomedicine

1 Introduction

Between the years 2000 and 2020, there was a decrease in deaths attributed to stroke, heart disease, and human immunodeficiency virus, whereas reported deaths from Alzheimer's disease (AD) saw a notable increase of over 145% (1). The incidence of deaths attributed to AD was further exacerbated in 2020 due to the global COVID-19 pandemic. Concurrently, the COVID-19 poses significant challenges and intricacies for caregivers of individuals with

dementia. During the past two decades, the primary therapeutic approaches for AD have encompassed interventions targeting anti-neurotoxic β -amyloid ($A\beta$) aggregates, anti-Tau, anti-neuroinflammatory, neuroprotective agents, and brain stimulation, among others (2–4). The accumulation and deposition of $A\beta$, particularly $A\beta_{42}$, serve as the primary and initiating etiological factor in the pathogenesis of AD (5, 6). Consequently, investigations involving $A\beta_{42}$ aggregates in both *in vivo* and *in vitro* settings have consistently formed the cornerstone of research in this area. Due to the metastability and heterogeneity of $A\beta$ (mainly $A\beta_{42}$) aggregates, the pathogenesis of $A\beta$ is inevitably diverse and complex (7, 8).

In recent years, there has been significant advancement in the field of nanotechnology, particularly in the development of emerging nanomaterials for the construction of nanoparticle-based drug delivery systems. This has garnered increasing attention in the fields of medicine and biology for their potential applications in disease diagnosis and treatment (9, 10). Nanoparticles exhibit a dense structure, enabling the attachment of drugs through mechanisms such as adsorption, dissolution, encapsulation, or covalent bonding (11–13). Nanoparticles have the capability to stabilize labile pharmaceutical compounds, enhance their aqueous solubility, extend the duration of drug or contrast agent presence in the circulatory system, and mitigate the inherent shortcomings of pharmaceutical compounds (14, 15). Furthermore, specialized targeting molecules can be employed to modify the nanoparticles for enhanced penetration of the blood–brain barrier, allowing for targeted action on specific cells or intracellular compartments (16, 17). Therefore, nanoparticles show great potential for enhancing pharmaceutical compounds delivery to specific central nervous system targets and facilitating pharmaceutical compounds release at sites of disease.

Polyphenols are commonly present in natural plant sources and exhibit diverse biological properties, particularly in the mitigation of AD and other neurodegenerative conditions (18, 19); however, their absorption and utilization within the human body are limited (20, 21). Hence, it is imperative to develop a strategy for harnessing the potential of polyphenols within the organism. This review provides an overview of the characteristics of amyloid and associated diseases, the inhibitory properties of natural polyphenols on amyloid fibrils, and the therapeutic effects and potential applications of polyphenol-based polymer nanoparticles.

2 Amyloidogenic property and diseases

Proteins are fundamental biomolecules that constitute the building blocks of life, serving as essential components for executing biological functions within organisms and contributing to various physiological processes. The preservation of proper protein structure is essential for the normal physiological functioning of proteins. Any deviation from the correct structure of a protein molecule is likely to result in the impairment of its function and the onset of organic pathology (22). Amyloid refers to a series of fibrillar proteins with abnormal protein conformation due to misfolding, which tend to aggregate with each other and form insoluble amyloid fibrils that are deposited in the body, thus triggering diseases, i.e., clinically recognized protein conformation diseases (23, 24). Currently, there exist over 20 types of protein conformational diseases, such as the

association of Type 2 diabetes (T2D) with pancreatic islet amyloid polypeptide; AD with Tau protein and β -amyloid protein (25, 26); Parkinson's disease with α -nucleosynthetic protein (27, 28); and transmissible spongiform encephalopathy with prion protein; Huntington's syndrome with polyglutamine aggregation, among others (29). The amyloid proteins associated with each of these diseases have fibrillar properties in a β -folded structural conformation and are deposited intracellularly or extracellularly to form amyloid plaques (30).

The investigation of these amyloid-related diseases has emerged as a prominent area of pharmacological research. These type of disease share the following common characteristics: (1) while the sequences of individual proteins may vary, the resulting aggregated properties exhibit a high degree of similarity, characterized by a structured and insoluble nature; (2) the formed aggregates contain a large amount of β -folding structure. These type of diseases are commonly classified under the umbrella term of amyloidosis (31–33). Proteinaceous deposits with a starch-like appearance accumulate in various organs and tissues, leading to the formation of insoluble aggregates that are typically detectable through Congo red staining (34). Various factors, including genetic predisposition, environmental influences, and individual behavior, can contribute to the development of amyloidosis. In addition to traditional diagnostic methods, physicians may employ live tissue sectioning techniques to assess the presence of amyloid proteins within affected tissues (35). Although amyloid proteins possess similar pathogenic characteristics, their distribution within the body may differ, resulting in unique clinical presentations (36).

2.1 Islet amyloid polypeptide and T2DM

Diabetes mellitus is a chronic metabolic disease characterized by abnormally high blood glucose concentrations, and it is widely recognized that diabetes mellitus is genetically determined and triggered by acquired factors. Diabetes mellitus is often associated with serious complications, such as blindness, dyslipidemia, cardiovascular disease and renal failure. Currently, type 2 diabetes mellitus (T2DM) presents a significant global health concern, with the Centers for Disease Control and Prevention reporting approximately 40 million individuals in the United States affected by pre-diabetic conditions (37). A study conducted in the U.S. investigating the efficacy of lifestyle modifications or metformin in preventing the progression of impaired glucose tolerance (IGT) to diabetes revealed that 11% of individuals with IGT transition to diabetes annually, resulting in an estimated 2–4 million new cases of diabetes each year (38). A recent study predicts that the global prevalence of diabetes will increase from 2.8% in 2000 to 4.4% in 2030, meaning that nearly 366 million people will develop T2DM (39).

Human islet amyloid polypeptide is secreted by pancreatic islet β -cells and contains 37 amino acid residues, referred to as hIAPP37 (40). The aggregation and formation of amyloid fibril aggregates of human islet amyloid polypeptide have been shown to have deleterious effects on pancreatic islet cells, leading to damage and ultimately contributing to the development of T2DM (41, 42). The facile formation of toxic amyloid fibril aggregates is a prominent pathological characteristic of T2DM. After conducting numerous clinicopathologic experimental studies on patients with T2DM, it was determined that a significant proportion of individuals exhibited

human pancreatic amyloid aggregates within the pancreatic islets, constituting approximately 90% of the total patient population. Conversely, human pancreatic islet amyloid aggregates were identified in only 15% of pancreatic islets in elderly individuals without diabetes mellitus symptoms (43).

Normally, insulin and islet amyloid polypeptides are co-secreted in response to blood glucose stimulation. In the atypical scenario of insulin resistance, the heightened demand for insulin prompts an elevation in insulin secretion, consequently resulting in an augmented co-secretion of islet amyloid polypeptide (44). It has been shown that the concentration of islet amyloid polypeptide in the blood during this process increases from the normal 1–20 pM to 50 pM (45), and the increased concentration puts the risk of generating amyloid deposits at an increased risk. The aggregates generated cause damage to the islet cells, which in turn exacerbates the insulin deficiency, and a vicious circle is set in motion.

2.2 β -amyloid peptide and AD

The AD is a neurodegenerative disease that occurs when the intelligence of the cerebral hemispheres of the brain, such as memory, language and reasoning, is in an impaired state (46). This degenerative brain disease, characterized by neurodementia, is considered a significant health concern impacting human longevity in contemporary society (47). Globally, the number of AD patients has now exceeded 30 million and is increasing by about 5 million per year, and it is expected that by 2040, the number of people suffering from AD will be more than 80 million, and the number in China will reach about 15 million, which is a three-fold increase compared with the beginning of this century (48). The disease is anticipated to impose significant economic strain and distress upon the families of afflicted individuals, thereby escalating into a pressing social issue of great concern.

The AD patients have two main types of abnormal lesions in the brain: (1) the presence of neurofibrillary tangles (NFTs) in the nerve cells of the brain, and (2) the appearance of age spots in the brain (49, 50). The primary components of the two lesions are abnormally phosphorylated Tau protein and β amyloid polypeptide, which is derived from the hydrolysis of an amyloid precursor protein called APP. APP contains a total of 770 amino acids, and its transmembrane region is capable of becoming a component of amyloid deposition through shearing (51). Another major pathology of NFTs is the formation of paired helical filaments (PHFs), which are mainly composed of hyperphosphorylated Tau protein (52). The number of NFTs in a patient's brain has been reported to be a very important indicator of the severity of AD.

2.3 Nguyen virus protein and spongiform encephalopathy

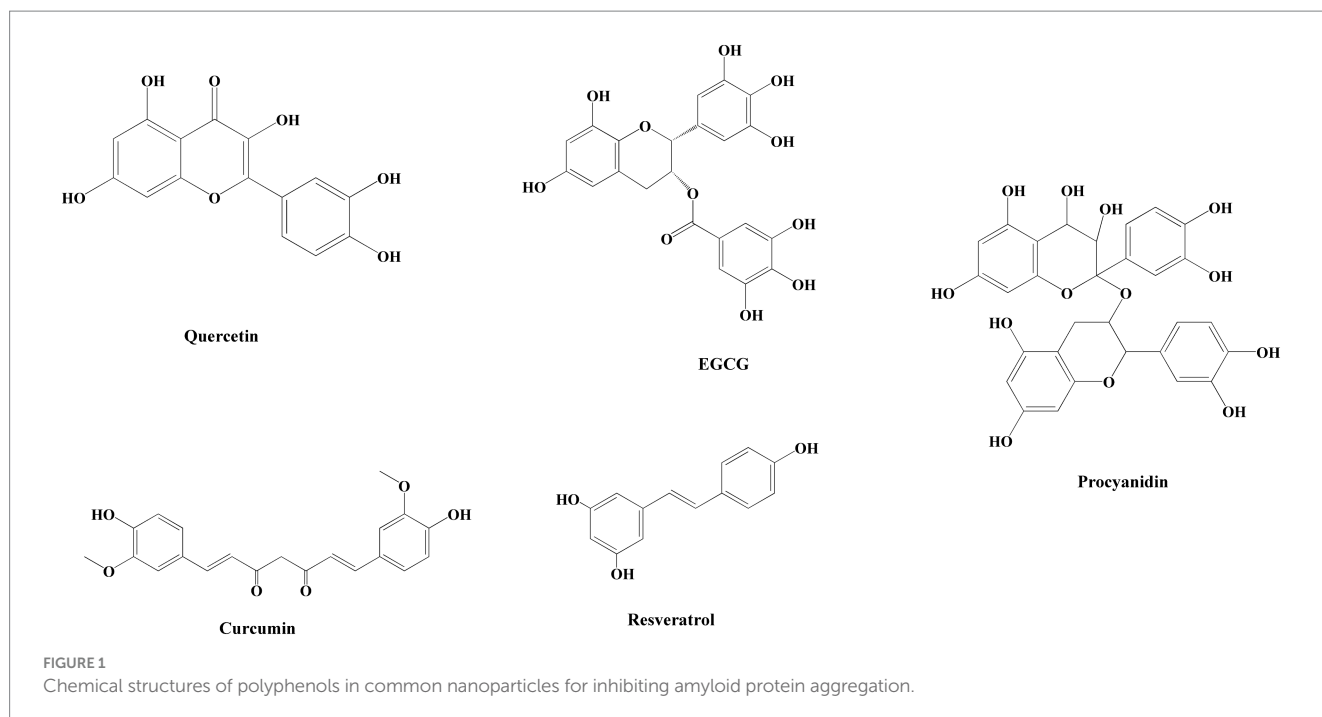
Transmissible spongiform encephalopathies (TSEs) are fatal neurodegenerative diseases affecting both animals and humans, characterized by the presence of an infectious agent known as the self-expressed structurally abnormal Prion protein (53). Examples of such diseases include Mad cow disease, Creutzfeldt-Jakob disease, and prurion in sheep (54). The pathology of TSEs is characterized by

the accumulation of amyloid plaque deposits, leading to degeneration, loss, vacuolar degeneration, death, and disappearance of neuronal cells in the cerebral cortex. This process ultimately results in the replacement of affected cells by vacuoles and stellate cells, causing a spongy state characterized by thinning of the cerebral cortex (gray matter) and relatively pronounced white matter, hence the term spongiform encephalopathy (55). Prion proteins (Prions) are a class of small molecule non-immunogenic hydrophobic proteins that can infect animals and replicate in host cells. The Prions molecule is incapable of inducing disease in its original form; rather, it must undergo a conformational change in order to adopt the infectious prion conformation and subsequently inflict damage upon neurons (56). Prions have the ability to induce conformational alterations in normal prion proteins, leading to their aggregation and subsequent interaction with additional normal prion proteins, ultimately resulting in a cascade effect that culminates in neuronal cell apoptosis (57). Normal Prion are present in both humans and animals and are labeled as PrP^C proteins, and Prions that are not normally present in the body but are infectious are labeled as PrP^{Sc} (58). There is a specific hydrophobic sequence, the 106–126 fragment (denoted as PrP¹⁰⁶⁻¹²⁶), in the ryanovirus protein. This sequence has an important role in the conversion of PrP^C to PrP^{Sc} and in the generation of associated neurotoxicity (59). PrP¹⁰⁶⁻¹²⁶ is frequently utilized as an *in vitro* model to investigating the aggregation process and pathomechanisms of Prions proteins due to its structural similarities with PrP^{Sc}, including a high prevalence of β -folded structures, propensity for aggregation to resist protease degradation, and significant cytotoxicity. To date, extensive research has been conducted on Prions and the PrP¹⁰⁶⁻¹²⁶ model; however, the precise mechanism underlying PrP^{Sc}-induced cytotoxicity and the pathogenic basis of aggregation remain elusive.

3 Amyloid fibrillation inhibition by natural polyphenols

Toxic amyloid fibrils pose a significant threat to human health, yet a definitive treatment remains elusive. Up to now, researchers have screened dozens of inhibitors, which are broadly categorized into three groups: peptide inhibitors, antibodies, and small molecule inhibitors (60). Peptide inhibitors and antibodies offer the potential for targeted therapy; however, their limited utilization is primarily attributed to issues related to stability and cost. Small molecule inhibitors exhibit advantageous pharmacological properties and minimal cytotoxicity, with a wide range of natural polyphenol inhibitors standing out as particularly notable in this aspect (61, 62). The structural formulae of common polyphenols for inhibiting amyloid protein aggregation are depicted in Figure 1. Furthermore, certain natural polyphenols not only hinder amyloid fibril formation but also demonstrate neuroprotective properties, including the mitigation of neuroinflammation, resistance to oxidative stress and apoptosis, restoration of mitochondrial damage, and enhancement of fibril deposit clearance (63, 64).

Natural polyphenols have shown promising results in the treatment of a number of age-related diseases. Epigallocatechin gallate (EGCG) is a natural polyphenol compound found in green tea. It has been reported in the literature that the anti-amyloid effect of EGCG has been identified in SH-SY5Y neuronal cells and AD rat model in 2007 (65, 66). It has been shown that EGCG can convert the A β and α -synuclein touch nucleoprotein mature protofibrils and toxic oligomers into



non-toxic small protein aggregates (67). Engel et al. (68) and Palhano et al. (69) have demonstrated that EGCG can inhibit hIAPP aggregation through hydrophobic effects. Resveratrol is also a natural polyphenol that is particularly abundant in grapes, and it is a natural non-flavonoid polyphenol that protects the cardiovascular system and prevent atherosclerosis (70). Resveratrol is also capable of directly interfering with amyloid aggregation of different peptides and reducing their toxicity (71). One study found that resveratrol effectively suppresses hIAPP aggregation via inhibiting the early formation of oligomeric intermediates (71). Resveratrol was also found to dose-dependently inhibit A β peptide amyloid fibrillation (72) and lysozyme amyloid fibrillation (73), and to break down already mature amyloid fibrils.

Curcumin, a polyphenol compound consisting of a β -diketone structure and two o-methylated phenols is derived from turmeric and has been utilized in traditional Chinese and Indian medicine for centuries (74). The significant curcumin content found in curry has been linked to a decreased risk of AD in the Indian population, as well as beneficial effects on cognitive function in elderly individuals (75). Traditional Chinese medicines such as turmeric (*Curcuma longa*) and *Poria cocos* contain abundant curcumin. Curcumin exhibits neuroprotective properties by inhibiting the aggregation of A β peptides, thereby altering the structure of A β fibrils and ameliorating the toxic effects induced by A β oligomers and the formation of non-toxic A β oligomers (76). Tannic acid possesses numerous hydroxyl and functional groups, enabling it to engage in interactions with diverse proteins, and these interactions can function as inhibitors of β -site amyloid precursor protein cleaving enzyme-1 (BACE1), A β , and Tau proteins (77).

4 Formation of polyphenol-based polymer nanoparticles

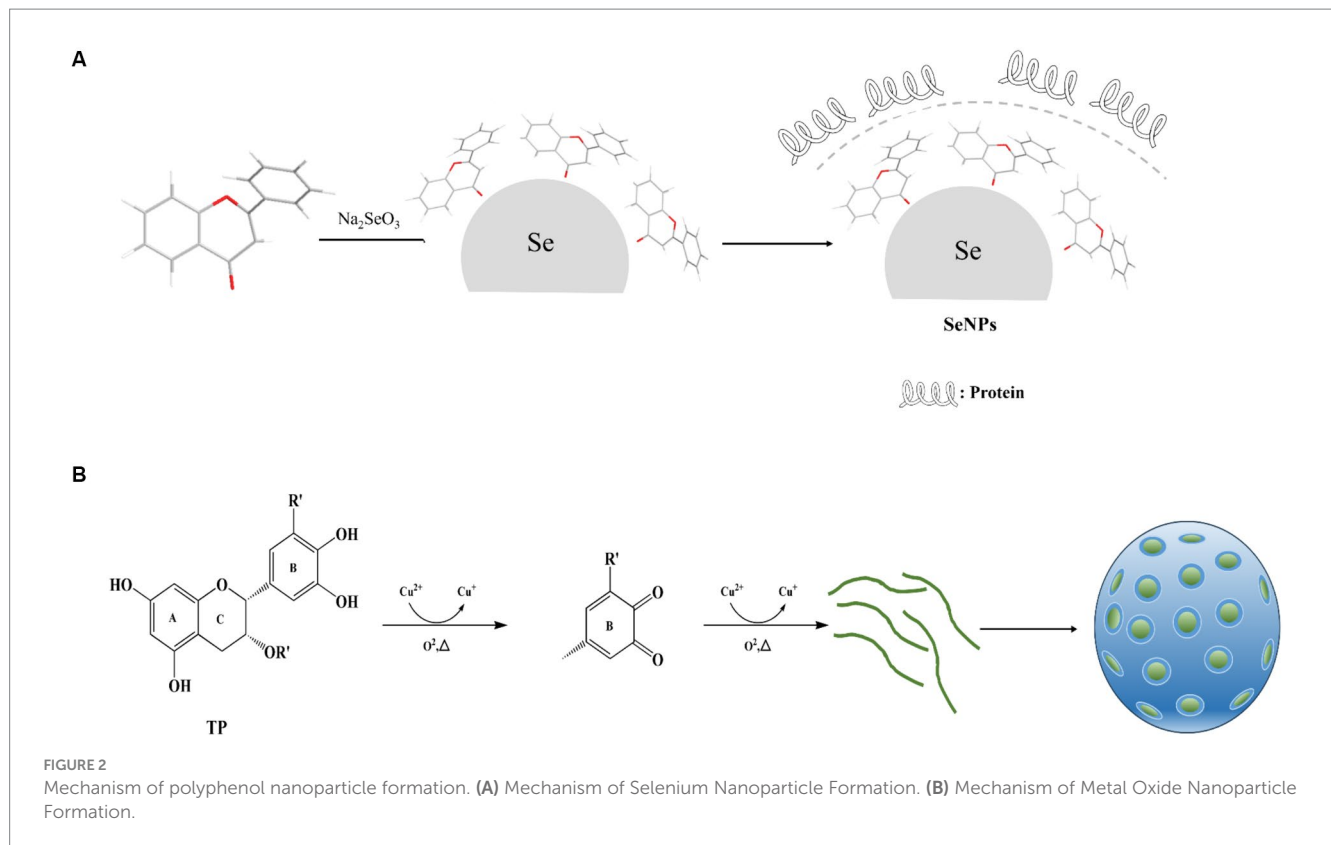
Polyphenols have garnered significant interest due to their distinctive physicochemical characteristics (78–81). Polyphenols can

be categorized into different groups based on the number of phenolic rings they contain and the underlying structural elements that bind these rings, and can be classified into several subclasses such as phenolic acids, flavonoids, stilbenes, and lignans (82), where flavanones, flavonoids, flavonols, anthocyanins, and phenolic acids contain at least one benzene ring, aldehyde group, and several phenolic hydroxyls (83), which are essential structural components that facilitate the biological activity of polyphenols.

Numerous polyphenols exhibit limited water solubility and are vulnerable to environmental factors, leading to diminished bioavailability. The incorporation of composite nanoparticles has been shown to enhance the encapsulation efficiency of polyphenols and contribute to the improved stability of these bioactive compounds (84).

Polyphenols possess distinctive structural and chemical characteristics, notably the inclusion of functional groups such as catechol and gallophenol groups, enabling them to engage in diverse non-covalent and covalent interactions with a broad range of materials. These interactions make polyphenols applicable in various fields, encompassing inorganic materials like metal ions, metals, metal oxides, semiconductors, carbon, and silicon dioxide, as well as organic materials such as small molecules and synthetic polymers, and even bioactive biomolecules and active microorganisms (85–87) (Figure 2).

Such as, Sorasitthyanukarn et al. (88) prepared chitosan/sodium alginate nanoparticles loaded with curcumin glutaric acid by O/W emulsification and ionization gelation, and optimized the conditions using response surface methodology, and the obtained products The study showed that curcumin glutaric acid-loaded chitosan/sodium alginate nanoparticles exhibited favorable stability, controlled release properties, and enhanced activity against multiple cancer cell lines. Zhou et al. (89) synthesized metal polyphenol nanoparticles using EGCG in aqueous solution with CuCl₂ with low toxicity and high biocompatibility, improved lysosomal escape efficiency by doping with cell membrane-penetrating peptides, and achieved targeted delivery to mitochondria. In addition, Ma et al. (90) used Cu²⁺ chelated EGCG



nanoparticles for the purpose of functionalizing collagen scaffolds into a spherical configuration. This structure exhibits slow release properties and possesses the capacity to scavenge free radicals, exhibit anti-inflammatory effects, inhibit bacterial growth, and promote angiogenesis.

5 Anti-amyloidogenic effects of polyphenol-based polymer nanoparticles

5.1 Green tea polyphenol-based nanoparticles

Green tea polyphenols consist of a diverse range of polyphenols present in green tea, with catechins constituting 70%~80% of the overall polyphenol composition. The four main types of catechins found in green tea are epicatechin, epigallocatechin, epigallocatechin gallate, and EGCG. Among these, EGCG is the most abundant and bioactive compound in green tea, and has been extensively researched in inhibiting amyloid fibrillation and has been observed to reduce amyloid cytotoxicity induced by Huntington's protein, alpha-synuclein, and A β (91–93). EGCG was found to directly bind to unfolded proteins and prevent the formation of β -sheet structures, which is an initial step in the cascade leading to amyloid formation. At the molecular level, autoxidized EGCG reacts with free primary amine groups of proteins to form Schiff bases and induce protofibril remodeling (94). The catechol structure of EGCG confers metal chelating, anti-inflammatory, antioxidant and neuroprotective activities that are crucial in the therapeutic management of AD (95).

Debnath et al. (96) synthesized a 25 nm EGCG nanoparticle that was 10–100 times more efficient than native EGCG in inhibiting protein aggregation, breaking down mature protein aggregates, and reducing amyloidogenic cytotoxicity. This result suggests that EGCG-based polymer nanoparticles are more potent in preventing and treating protein aggregation-derived diseases. Zhang et al. (97) attached EGCG to selenium nanoparticles (EGCG@Se) and synthesized EGCG-stabilized selenium nanoparticles encapsulated with a Tet-1 peptide (Tet-1-EGCG@Se). EGCG@Se and Tet-1-EGCG@Se could label A β protofibrils with high affinity and the Tet-1 peptide could significantly enhance the cellular uptake of Tet-1-EGCG@Se in PC12 cells. In addition, studies have been conducted to prepare EGCG-derived carbonized polymer dots, and the prepared polymers interacted with A β through hydrogen bonding, electrostatic interactions, and hydrophobic interactions, leading to alterations in the A β aggregation pathway. It provides an important reference for the development of multifunctional EGCG-based polymer nanomaterials against neurodegenerative diseases and other protein conformation diseases (98).

5.2 Curcumin-based nanoparticles

Turmeric is widely produced in India as well as Pakistan, Bangladesh, China, Indonesia and Pakistan South America. The most active component of turmeric is curcumin, which makes up 2–5% of the spice (99). Numerous studies have demonstrated that curcumin can effectively inhibit amyloid fibrillogenesis. Such as, Pal et al. (100) explored the inhibition of amyloid fibrillogenesis by Al(III) and Zn(II) curcumin mixtures, and the results showed that

metal-curcumin mixtures can inhibit the transition of oligomers to β -sheet protofibrils, and Al(III)-curcumin mixtures than Zn(II)-curcumin mixture was more effective in inhibiting β -protein aggregation. In addition, experimental evidence has shown that curcumin has the ability to inhibit the formation of A β amyloid fibrils by modifying the structure of protofibrils and altering the aggregation pathway of protofibrils (101).

Furthermore, native curcumin can inhibit the formation of amyloid fibrils by inhibiting the generation of primary nuclear structures of amyloid peptides through hydrogen bonding, hydrophobicity, and cationic tightness to A peptides (102). Brahmkhatri et al. (103) successfully synthesized curcumin-coated polymeric gold nanoparticles (PVP-C-AuNP) that demonstrated inhibition of A β_{1-16} aggregation by targeting the n-terminal region of A β amyloid peptide, and this study revealed that PVP-C-AuNP exhibited the ability to degrade mature amyloid fibrils. Mirzaie et al. (104) prepared methoxy polyethylene glycol polymer nano colloids with/without curcumin as phosphatidylethanolamine-stearoyl, and then explored their effects on the amyloid fibrillation process of bovine serum albumin, and the results showed that curcumin-loaded nano colloids had an inhibitory effect on the formation of amyloid fibrils. Research has also been conducted on the potential inhibition of amyloid fibrillation through structural modifications of curcumin. Solid lipid curcumin particles (SLCP) provide an alternative strategy for curcumin delivery, and intraperitoneal injection of SLCP in AD mice demonstrates superior therapeutic effectiveness compared to the free curcumin. Specifically, the lipid bilayer of SLCP facilitated crossing the blood-brain barrier. Within the brain, SLCP was found to bind to A β plaques in the prefrontal cortex and dentate gyrus, resulting in a decrease in the formation of A β_{42} oligomers and protofibrils, while also improving neuronal morphology (105). Giacomeli et al. (106) prepared curcumin-loaded lipid core nanocapsules (LNC) that demonstrated notable neuroprotective properties in mitigating A β_{1-42} -induced behavioral and neurochemical alterations in an AD model.

5.3 Resveratrol-based nanoparticles

Resveratrol is a polyphenolic compound widely found in grapes, tiger nuts, peanuts, cassia and other plant foods or medicines, and is a fat-soluble plant antitoxin derived from plants (107, 108). Resveratrol exhibits a diverse array of physiological effects, including inhibition of cell membrane lipid peroxidation, protection against cardiovascular disease, anti-inflammatory properties, neuroprotection, and estrogenic activity (109, 110). Recently, nanoparticles have been used as effective carriers to enhance the oral bioavailability of resveratrol (111). Selenium nanoparticles functionalized on the surface of 100 nm resveratrol has been shown to be more effective than native resveratrol in inhibiting A β aggregation and reactive oxygen species (ROS) formation (112). Li et al. (113) prepared resveratrol-selenopeptide nanocomposites that interacted with A β , reduced A β aggregation, effectively inhibited A β deposition in the hippocampus, ameliorated cognitive deficits; and reduced A β -induced ROS and enhanced antioxidant enzyme activities in PC₁₂ cells and *in vivo*; and also reduced A β -induced neuroinflammation in BV-2 cells and *in vivo* by regulating nuclear factor κ B/mitogen-activated protein kinase/Akt signaling pathway to reduce A β -induced neuroinflammation in BV-2 cells and *in vivo*. Yang et al. (114) prepared resveratrol-loaded

selenium nanoparticles/chitosan nanoparticles, which could alleviate cognitive deficits by restoring the balance of the intestinal flora, and thus suppress oxidative stress, neuroinflammation, and metabolic disorders in AD mice.

5.4 Anthocyanidin-based nanoparticles

Anthocyanidin are polyphenolic compounds found in fruits, grains, and flowers with antioxidant, anti-inflammatory, and anti-apoptotic properties (115, 116). Previous studies have shown that anthocyanins extracted from Korean black soybeans prevent neuroinflammation, neuronal apoptosis, and neuronal degeneration (117, 118). The findings indicate that anthocyanins may hold therapeutic potential for neurodegenerative disorder. Amin et al. (119) encapsulated anthocyanins in biodegradable nanoparticle formulations based on poly (lactide-co-glycolide) (PLGA) and stabilizer polyethylene glycol (PEG)-2000 delivery system. The findings demonstrate the therapeutic promise of anthocyanins in mitigating Alzheimer's disease pathology and suggest that the efficacy of anthocyanins can be enhanced by utilizing nanomedicine delivery systems. Kim et al. (120) encapsulated anthocyanins in polyethylene glycol functionalized AuNPs, which were coupled with PEG AuNPs to enhance A β_{1-4} injecting the bioavailability of mice and controlling the release of anthocyanins. Kim et al. (120) prepared PEG-AuNPs loaded with anthocyanins that reduced A β_{1-42} -induced markers of neuroinflammation and apoptosis through inhibition of the p-JNK/NF- κ B/p-GSK3 β pathway, and were more potent with PEG-AuNPs than with native anthocyanins alone. These results imply the possibility of PEG-coated AuNPs loaded with anthocyanins as therapeutic agents for neurodegenerative diseases, especially AD.

5.5 Quercetin-based nanoparticles

Quercetin is a flavonoid found in many vegetables and fruits and Traditional Chinese medicine such as white onion bulbs, lingonberries, cranberries, Kudzu root, and *Polygonum multiflorum* (121–123). Quercetin exhibits promise in attenuating the advancement of degenerative neurological disorders through the modulation of cellular pathways associated with A β -induced neurotoxicity and the alleviation of its adverse effects on neuronal cell lines and neurons (124–126). Nevertheless, the limited water insolubility, and extensive metabolism of quercetin pose challenges to its biological utility. A recent study has demonstrated that quercetin released from the nano-preparation maintains its biological activity by preparing quercetin-loaded modified core-shell mesoporous silica nano-preparations having a polyethylene glycol 3,000 surface-modified magnetite core that interferes with the aggregation of A β peptide and reduces the cytotoxicity of A β and the A β -induced generation of ROS (127). An additional method of encapsulating quercetin within lipid nanoparticles has been developed to produce a nano-system that is functionalized with transferrin, enabling the targeted delivery of quercetin to the brain. This approach has shown enhanced efficacy in inhibiting A β aggregation while maintaining minimal cytotoxic effects (128). The utilization of quercetin-based nanoparticle systems presents a novel approach to enhance current therapeutic interventions, offering compelling evidence and renewed optimism

for the treatment of Alzheimer's disease through quercetin administration.

6 Potential opportunities of polyphenol-based polymer nanoparticles

In recent years, nanotechnology-based pharmaceutical compounds delivery systems have received much attention for their potential to prolong drug residence and circulation in the bloodstream as well as to enhance the stability and solubility of pharmaceutical compounds. Advantages of the nanoparticle form include increased water solubility of amyloid-targeting molecules and enhanced binding affinity to amyloid structures (96). Optimal nanoparticle should possess non-toxic and biodegradable properties, with additional consideration given to factors such as material composition, preparation technique, nanoparticle dimensions, and surface modifications, all of which significantly impact the successful targeted delivery of pharmaceutical compounds, including penetration into the central nervous system. The potential function of nanoparticles is to stabilize labile pharmaceuticals, enhance their water solubility, prolong the presence of drugs or contrast agents in the circulatory system, and address the inherent limitations of pharmaceutical compounds (129). The application of nanotechnology in polyphenols delivery systems improves the bioavailability and kinetic properties of natural polyphenols in biological systems, and advances in nanotechnology help to target natural polyphenols to specific sites or molecular targets and deliver natural polyphenols safely to specific sites of action, especially for natural polyphenols targeting the central nervous system, such as for AD. The sustained release of polyphenol-based polymer nanoparticle enhances the controlled release properties of the loaded polyphenols, thereby minimizing the dosage regimen, minimizing the (toxic) side effects of the polyphenol, and maximizing the safety, which greatly improves the applicability and feasibility of the natural polyphenols.

Furthermore, the utilization of polyphenol-based polymer nanoparticles to target the central nervous system enhances the efficacy of natural polyphenols in traversing the blood–brain barrier, resulting in a synergistic therapeutic effect. Thus, the sustained effectiveness of natural polyphenol candidates in the treatment of AD can be enhanced by polyphenol-based polymer nanoparticles. Currently, chitosan, poly (alkyl cyanoacrylate) (PACA), PLGA and polyethylene glycol-modified PLGA (PEG-PLGA) are the most commonly used polymers for polyphenol-based polymer nanoparticles applications. PEG-PLGA are the most commonly used polymers in polyphenol-based polymer nanoparticles applications and play a great auxiliary role in brain-targeted delivery of natural polyphenols as well as in improving natural polyphenols utilization. Currently, it is also important to prepare safe and effective polyphenol-based polymer nanoparticles.

7 Conclusion and perspectives

Dr. Alois Alzheimer first described AD in 1906, but there are still no appropriate therapeutic drugs to treat it. Moreover, in the context

of AD, existing treatments offer solely symptomatic relief and do not effectively halt the progression of the disease. No drug has been approved by the U.S. Food and Drug Administration for the treatment of AD since 2003. Therefore, it is important to improve the efficacy of currently available pharmaceutical compounds through the use of delivery technologies including nanomedicines and to develop new polymer nanoparticles that block all possible mechanisms of disease pathogenesis in order to treat patients with AD.

Natural polyphenols are widely found in plants in nature. Due to their diverse biological activities, including antioxidant, anti-inflammatory, and intestinal flora regulation properties, they are utilized in the food industry as primary nutritional components in functional foods (Figure 3). Numerous studies have shown that natural polyphenols effectively mitigate the deleterious impact of amyloid peptides on neuronal cells and neurons; however, these compounds are constrained by various limitations including the necessity for higher doses to achieve therapeutic efficacy, suboptimal absorption rates, restricted bioavailability, peripheral side effects, and challenges in traversing the blood–brain barrier. Natural polyphenols have the chemical property of providing both covalent and non-covalent bonds, and thus they have great potential for engineering materials applications to construct inorganic compound-phenolic fractions while generating functional polyphenol-based inorganic hybrid nanoparticles. In addition, by controlling and stabilizing the physicochemical interactions between molecules, polyphenols can not only self-assemble into particles in confined spaces, but also form coatings on the surfaces of preformed particles or serve as templates for the secondary growth of other functional materials. Thus, having special physicochemical properties makes polyphenols of practical use in various fields of polymer nanoparticles application.

The research on polyphenol-based polymer nanoparticles in inhibiting amyloid protein aggregation in the field of traditional Chinese medicine (TCM) also holds great potential (Figure 4). The major manifestations include: (1) development of TCM resources: TCM possesses abundant plant resources, many of which are rich in polyphenol. Through research on polyphenol in TCM, it is possible to develop polyphenol-based polymer nanoparticles that possess the capability to inhibit amyloid protein aggregation. (2) Application of polyphenol-based nanoparticles: TCM ingredients have been proven to possess the efficacy of inhibiting amyloid protein aggregation. The enhancement of therapeutic effects of TCM can be achieved through the preparation of polyphenol-based nanoparticles, which serve to improve the bioavailability and stability of the medications. (3) Compatibility application of TCM polyphenol-based nanoparticles: TCM emphasizes the compatibility of medications, aiming to enhance therapeutic effects through the combination of multiple pharmaceutical compounds. The incorporation of polyphenol-based polymer nanoparticles in conjunction with other TCM components has been shown to augment the suppression of amyloid protein aggregation. (4) TCM's multi-target treatment strategy: TCM focuses on the holistic concept and adopts a multi-target treatment strategy. Polyphenol-based polymer nanoparticles can interact with multiple targets, inhibiting abnormal aggregation of amyloid proteins and intervening in diseases related to amyloid proteins at multiple levels. (5) Personalized treatment: TCM emphasizes personalized treatment, providing targeted therapies based on the patient's constitution and condition. Polyphenol-based polymer nanoparticles can be customized according to the specific situation of the patient, offering personalized treatment plans.

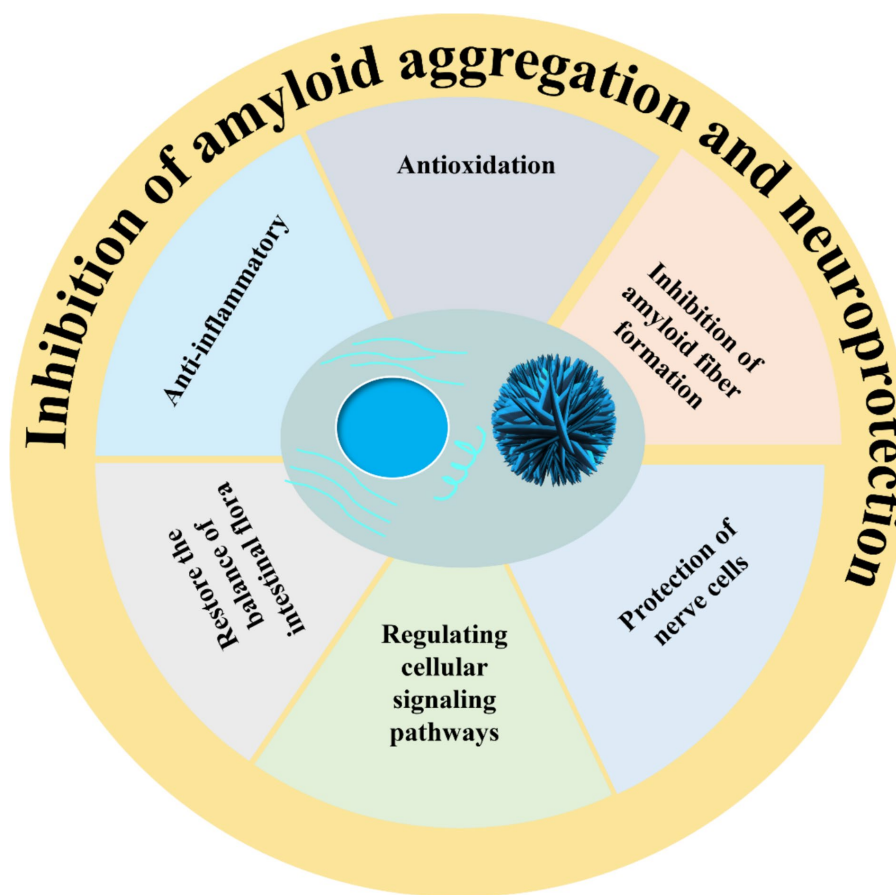


FIGURE 3
Pathways of polyphenols in inhibiting amyloid deposition and neuroprotective effect.

Although polyphenol-based polymer nanoparticles have shown potential in inhibiting amyloid protein aggregation in the field of TCM, further research and clinical experiments are still needed to verify their safety and effectiveness. Simultaneously, further research is needed to investigate the integration of TCM with modern scientific principles in order to advance the utilization of polyphenolic compounds for inhibiting amyloid protein aggregation in therapeutic applications.

Author contributions

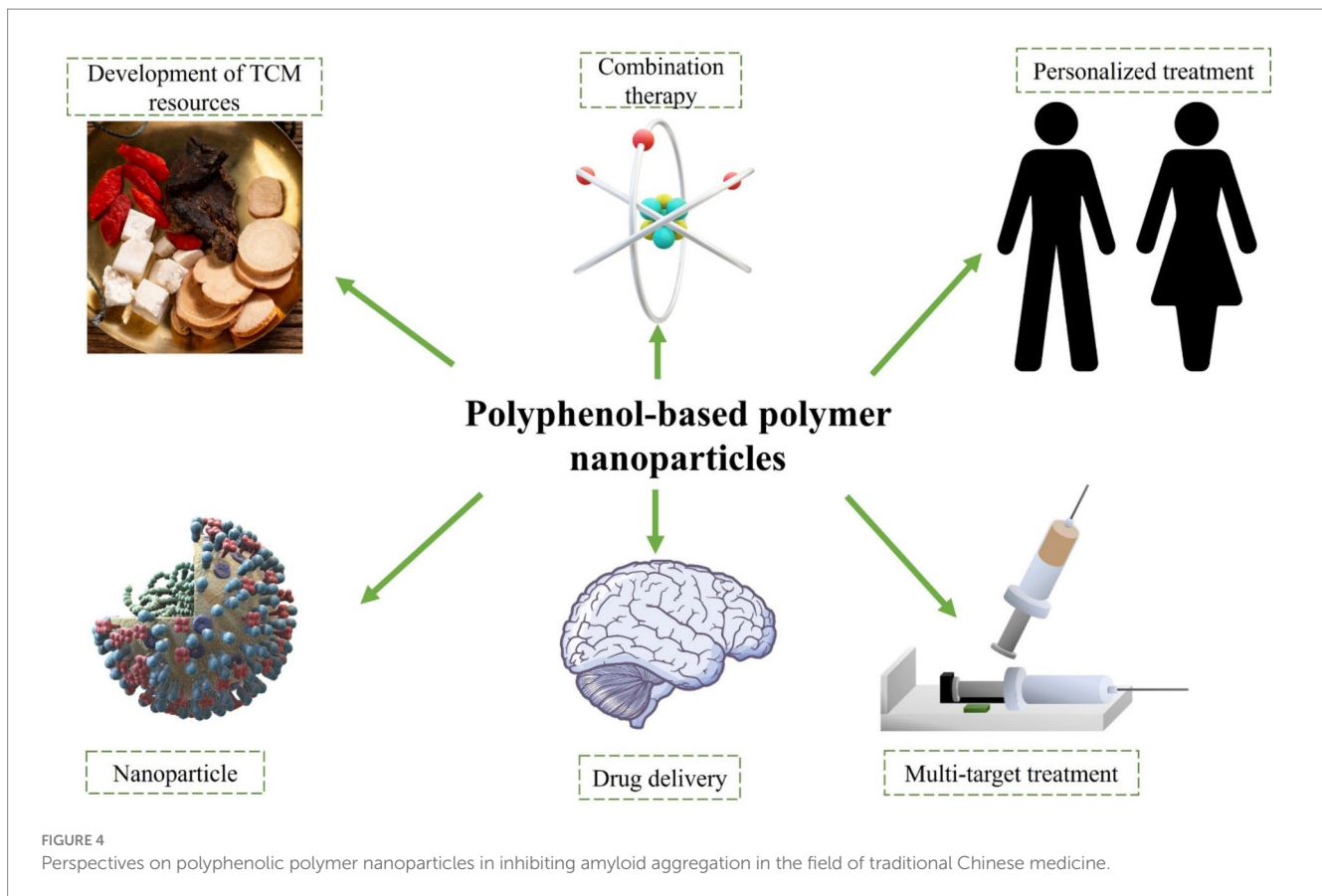
SF: Conceptualization, Investigation, Methodology, Validation, Writing – original draft, Writing – review & editing. KZ: Formal analysis, Software, Validation, Writing – review & editing. DL: Formal analysis, Methodology, Writing – review & editing. YY: Formal analysis, Writing – review & editing. HX: Methodology, Writing – review & editing. WX: Formal analysis, Writing – review & editing. KD: Funding acquisition, Writing – review & editing. ZR: Resources, Writing – review & editing. DW: Methodology, Supervision, Writing – review & editing. WY: Conceptualization, Funding acquisition, Resources, Supervision, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.



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