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Inhibition of amyloid beta oligomer, fibrils, and peptide using nanoparticles to disrupt Alzheimer's pathogenesis.

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Abstract

The Aβ peptide, which is connected to the development of Alzheimer's disease, forms highly neurotoxic prefibrillar oligomeric aggregates, which are challenging to study due to their fleeting, low prevalence, and diverse nature. These aggregates are considered to play a role in the pathogenesis of numerous neurodegenerative diseases. The potential approach of blocking or disrupting the buildup of amyloid peptides, particularly amyloid-β (AβOs), by using nanoparticles that specifically bind or prevent their aggregation to develop new medications and treatments for Alzheimer's disease (AD) could be a promising solution. Nanoparticles have been proposed as a potential solution to modify the protein fibrillation process. Recently, Researchers have design and created some nanoparticles for inhibition of amyloid-β oligomer and (Aβ) peptide aggregation, involved in Alzheimer's disease (AD). In this concise review, we concentrated on the mechanism and formation of amyloid beta oligomers, fibrils, peptides, and it's role in Alzheimer's disease. Secondly, we discussed small molecules that can detect various forms of amyloid beta for early diagnosis. Lastly, we primarily focused on nanoparticles that possess the ability to inhibit and disaggregate amyloid beta oligomers fibrils, and peptide which are the primary hallmarks of Alzheimer's disease. Here for the first time we also summarize some of the nanoparticles and nanomaterials which can dis-aggregate the exis-ting amyloid-β oligomer and (Aβ) peptide which are challenging for many researcher.

Keywords: Alzheimer's disease; Amyloid beta oligomer; Aβ peptides; Aggregation inhibitor; Nanoparticles; Inhibition of Aβ Peptide by nanoparticles**.**

1. Introduction

Alzheimer's disease, first identified by Alois Alzheimer in 1906, is a significant health issue due to its high prevalence and costly treatment options. Currently, approximately 6.7 million Americans over the age of 65 are affected by this condition, and this number is projected to reach 13.8 million by 2060 without effective treatments, prevention strategies, or timely diagnosis [1]. Despite extensive research into the pathogenesis of Alzheimer's Disease (AD), the underlying mechanisms remain largely unexplored. The disease is primarily characterized by complex patho-physiological processes. During the early stages, patients exhibit symptoms such as apathy, despair, and short-term memory loss, particularly in areas such as recall of names, events, and conversations. As the disease progresses, additional symptoms may arise, including loss of voice, mobility, difficulty swallowing, disorientation in time and space, confusion, impaired communication, and challenges with maintaining personal hygiene [2]. The deposition of plaques

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and tangles in the brain upon the misfolding of amyloid-β (Aβ) and hyperphosphorylated tau, respectively [3]. Since Aβ and tau abnormalities directly lead to neuronal loss, synaptic dysfunction, neuro-inflammation, atrophy, and cognitive impairments in AD, both proteins have been the primary targets for disease-modifying drug discovery [4,5,6]. Over the last thirty years, most efforts to find drugs for AD have concentrated on blocking the early pathogenic mechanisms of AD, such as the processing of amyloid precursor protein, kinase-mediated tau phosphorylation, and protein misfolding, which prevent the production, phosphorylation, and aggregation of tau and Aβ [7,8]. An accumulation of insoluble protein aggregates, mainly made up of neurotoxic amyloid-β (Aβ), is a pathological feature of AD. The production of Aβ results from the β- and γ-secretases cleaving the amyloid precursor protein (APP) in a sequential manner [9]. Among the various Aβ isoforms that are produced, Aβ40 and Aβ42 are the most physiologically significant, ranging in length from 39 to 43 residues. Aβ42 is more prone to aggregation than Aβ40, with a roughly 9:1 ratio found in AD patients [10]. As per the initial amyloid-cascade theory, Alzheimer's disease commences when soluble Aβ monomers transform into insoluble fibrils [11]. According to mounting data, some soluble Aβ oligomers and protofibrils are more harmful than Aβ fibrils, and dementia is substantially correlated with their presence [12,13]. Thus, one effective way to prevent Aβ-associated neurotoxicity is to reduce neurotoxic Aβ oligomers and protofibrils. The potential of several small molecules to control Aβ aggregation and lessen neurotoxicity has been investigated [14,15]. Congo red, an amyloid-structure specific dye, has the ability to modulate fibril formation and reduce Aβ neurotoxicity [16,17]. In addition to dyes specific to amyloid, a number of lipid-based modulators and polyphenols have been shown to control Aβ aggregation and lessen Aβ-related toxicity. These include scyllo-inocitol, curcumin, nordihydroguaiaretic acid, and EGCG [18,19]. Research indicates that the inhibition or aggregation of (Hsp70) is primarily responsible for its ability to promote tau and amyloid clearance [20,21]. Additionally, several other studies have identified tau aggregation inhibitors, although the ability of these compounds to facilitate tau clearance has not been extensively explored for the majority of these. Some examples of compounds that inhibit tau aggregation in vitro include phenols from olive oil, amino-thieno-pyridazine (ATPZ), rhodanines, and anthraquinones; however, it is unclear whether these actions are enough to promote tau reductions in living cells [22,23,24].

2. The pathology of Alzheimer's disease and amyloid-β oligomers.

After β-secretase (BACE1) or α-secretase (primarily ADAM10) cleaves APP, presenilin 1 (PS1) or PS2 or other γ-secretase complexes cleave the resulting C-terminal fragments generated by BACE1 and α-secretase, respectively, to produce Aβ and p3 peptide [25]. This is how Aβ is made from its precursor, amyloid precursor protein (APP). The relationship between Aβ and synapse failure in AD is explained by the Aβ oligomer hypothesis, according to more recent research, even though the Aβ cascade hypothesis is still generally accepted [26, 27]. Soluble assemblies of Aβ, known as Aβ oligomers (AβOs), are thought to cause neurotoxicity and synaptotoxicity, which in turn sets off the harmful cascades responsible for the typical pathologies associated with AD. Though AβOs come in a variety of sizes, the most toxic species are still unknown. Numerous studies, including our own, have shown that AβOs cause a range of pathological changes, such as oxidative stress, mitochondrial dysfunction, synaptic deficits, apoptosis, aberrant tau alterations, and cognitive impairments. These studies collectively lend support to the theory that AβOs bring about [28]. It is widely admit that AβOs are significantly more toxic than Aβfibrils [29]. AβOs are present in the AD brain tissues [30], and they are closely connected to Aβ plaque pathology in the AD brains. [31]. Research has shown that Aβ can prevent synapses from being overactivated and lessen the amount of synaptic excitotoxicity produced in a normal physiological setting [32, 33]. However, in pathological conditions, abnormal accumulation and aggregation of Aβ to form β-sheet-rich conformations occur due to increased production of Aβ or inhibition of clearance [34]. Soluble polymers known as oligomers are put together by monomers, some of which are intermediates in the formation of filaments. Different conformations and molecular weights of oligomers produce a range of oligomeric properties. Since there is strong evidence that Aβos contribute to the development of AD, understanding the molecular mechanisms underlying the aggregation of Aβ monomers into toxic Aβos is crucial to understanding the pathological mechanism of AD. When two or more monomers assemble via the fibril-dependent mechanism (secondary nucleation) or the fibril-independent pathway (primary nucleation), where Aβ monomers cluster prion-like on the surface of fibrils, Aβ aggregates are formed [35,36]. Soluble Aβ oligomers may result in a highly selective form of neuronal death, which is accelerated by increased exposure to these oligomers [37]. Additionally, research has demonstrated that soluble AβOs might directly cause neural signaling dysfunction, which would otherwise cause early memory loss and dementia in AD. Furthermore, AβOs quickly prevented synaptic long-term potentiation (LTP) in brain slices [38]. Certain aberrations in the structure, form, and concentration of synapses can be attributed to the detrimental effects of AβO, [39]. Another possible tactic is to use specific small molecules to lessen the intrinsic toxicity of AβOs. Actually, anumber of current pre-clinical investigations have supported the feasibility of the latter strategy [40]. The levels of AβOs in the brain increased exponentially in aging mice. In addition, the load of AβO deposits signifcantly correlated with fibrillar Aβ plaque de-position as well as with neuronal loss and numbers of astrocytes, although not with memory deficits. The astrocyte response, as represented by number of glial fbrillary acidic protein-positive cells, was related to memory impairment and neuronal cell loss On the other hand, there was no relationship found between the total amount of Aβ plaque and the number of astrocytes or

neurons [41]. Today, AβOs are widely regarded as the most toxic and pathogenic form of Aβ [42,43]. It is important to reduce the toxicity of AβOs and Tau NFT, On the other hand, phytochemicals have anti-oxidant and anti-inflammatory properties which can combat a variety of pathological issues; they may be used as therapeutic agents to treat AD neuro-degeneration. Many phytochemicals have been shown to control Aβ aggregation and disrupt the amyloid cascade. Phytochemicals' anticholinergic, antioxidant, and inflammatory qualities have led to the discovery of possible treatment benefit for AD [44].

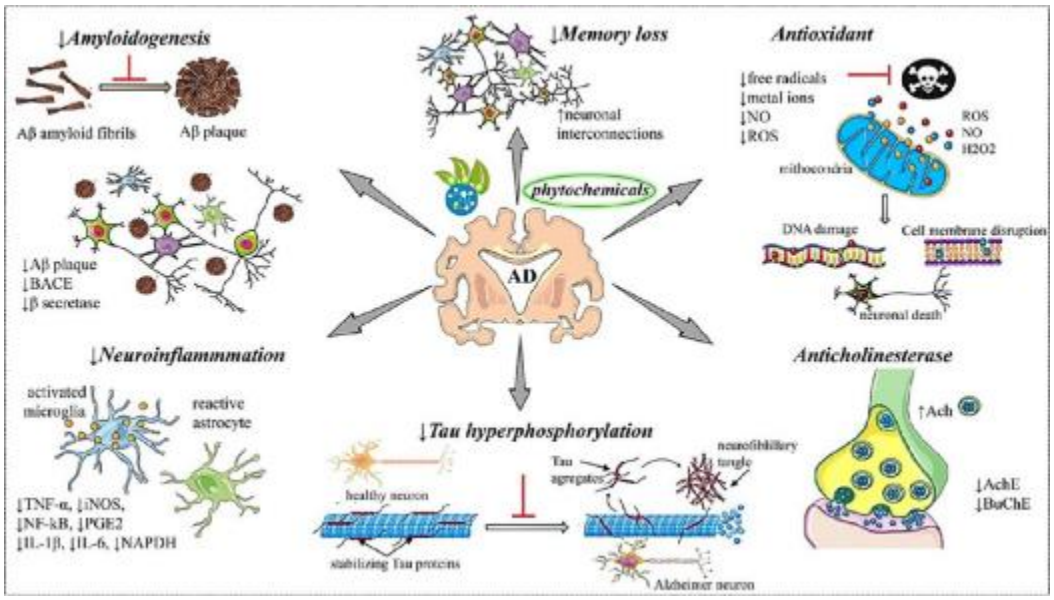

Figure 1 An explanation of how phytochemicals affect AD and the most common neuroprotective mechanisms is shown below. Abbreviations and symbols used include acetylcholine (ACh), acetyl-choline-sterase (AchE), amyloid-beta (Aβ), beta-site amyloid precursor protein cleaving enzyme 1 (BACE1), butyryl-choline-sterase (BuChE), inducible nitric oxide synthase (iNOS), Tumour necrosis factor (TNF)-α, interleukin (IL), nitric oxide (NO), nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), prostaglandin E2 (PGE2), nicotinamide adenine dinucleotide phosphate (NADPH), reactive oxygen species (ROS), and TNF-α are all involved in the process. Adopted from ref [44].

2.1. Structure and mechanism of oligomer formation

In AD, amyloid-β Aβ mis-fold and form oligomers and fibrils that accumulate in the brain in pathogenic pathways leading to synaptic loss and selective neuronal death (Figure 2) [45]. Aβ monomers self-assemble into various morphologies, including oligomers, pre-fibrils, and fibrils. Oligomers are soluble and diffuse throughout the brain, whereas fibrils are insoluble and can aggregate into amyloid plaques [46]. The outcome of the solid-state nuclear magnetic resonance (NMR) test revealed that the mature fibrils possess a highly organised and stiffer structure as compared to the monomers and oligomeric forms of Aβ. [47]. Infrared spectroscopy has revealed that the secondary structure of Aβ comprises a β-turn and two anti-parallel β-sheets. Furthermore, hydrophobic interactions play a crucial role in the aggregation of Aβ, leading to both inter-molecular and intra-molecular interactions between the hydrophobic regions of the Aβ peptide [48].The formation of amyloid fibrils involves the aggregation of monomeric Aβ into soluble oligomers, which are intermediate steps in the process. Unlike monomers and protofibrils, little is known about Aβ oligomers because amyloid assembly is an equilibrium reaction, making intermediates difficult to stabilize. Aβ monomers can form various oligomers, ranging from dimers to dodecamers, through a highly ordered process. Oligomers are classified based on the number of aggregated monomers as either low-n (2-4 dimers) or high-n (12-48 mers), with megamers representing even larger bodies. They can also be categorized by shape: spherical, prefibrillar, and annular [49]. Two or more monomers can come together to create Aβ fibrils through either a primary nucleation process known as the fibril-independent pathway or a secondary nucleation process known as the fibril-dependent mechanism. The process of aggregation typically involves three distinct stages: the lag phase, the growth phase, and the stationary phase [50]. Amyloid fibrils feature a layered arrangement of protofibrils, each about one micrometer long and several nanometers wide. These protofibrils are aligned side by side, with beta strands in each protofibril stacked perpendicular to the fibrils' long axis, creating a cross-beta structure through a network of hydrogen bonds [51]. Moreover, it has accomplished numerous outstanding outcomes. The complete Aβ molecule contains the shortest fibrillar component, Aβ16-22, which serves as a crucial model for examining amyloid fibril development. The β-sheet structure of Aβ16-22

fibrils was uncovered through solid-state NMR measurement, suggesting that the molecular structure of fibrils is similar to that of the peptide [52].

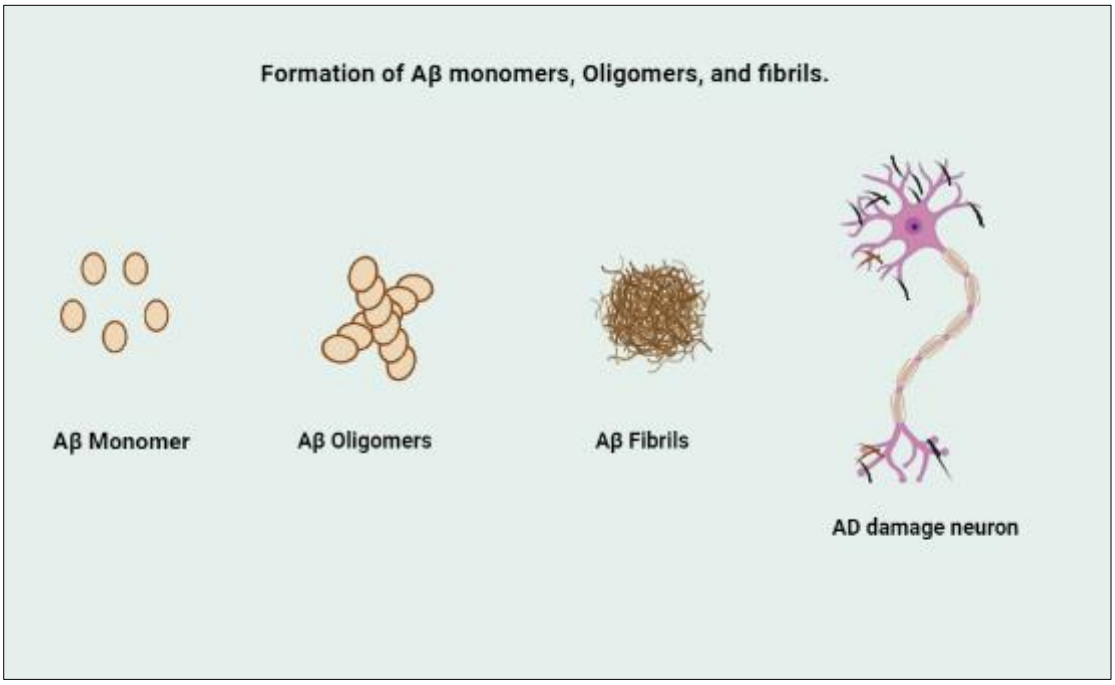

Figure 2 Mechanism of Formation of amyloid beta monomer, oligomers, fibrils, and it roles in neuron.

2.2. Detection of amyloid-β oligomers, fibrills and plaques by small molecules fluorescent probes.

In recent years, considerable effort has been dedicated to investigating methods for detecting Aβ plaques in the brain using neuro-imaging. A variety of imaging techniques have been utilized, such as positron emission tomography (PET) [53,54,55]. Currently, numerous fluorescent probes have been reported for the detection of Aβ. The vast majority of these probes are unable to breach the blood-brain barrier (BBB), which greatly limits their utility for detecting Aβ in vitro [56]. Therefore, it is of great significance to design Aβ probes that can be used for in vivo imaging [57]. In the creation of Aβ imaging probes, several luminescent materials are noteworthy due to their exceptional photophysical properties, including curcumin and 4,4-difluoro-4-bora-3a,4a-diaza-s-indacene (BODIPY), among others [58]. These dyes can bind to the hydrophobic cavities of Aβ, causing their fluorescence to light up and mapping the location of Aβ deposits in the brain [59]. Early detection is crucial for subsequent effective intervention; how-ever, current diagnostic methods may lack the necessary sensitivity to detect the dis-eases in their initial stages [60]. From a disease diagnosis viewpoint, fluorophores and dyes, including Thioflavin T (ThT),Thioflavin S (ThS), 8-anilinonaphthalene-1-sulfonic acid (ANS),and Conge red [61,62]. have been developed for amyloid detection and sensing. These sensing molecules have exploited their fluorescence properties for monitoring the conformational change and aggregation of amyloid proteins [63,64]. These sensing molecules typically exhibit enhanced fluorescence upon binding to β-sheet-rich fibrils, enabling to monitor and quantify amyloid formation. However, fluorescent molecules commonly used in amyloid detection and sensing exhibit several shared limitations: (i) susceptibility to the aggregation-caused quenching(ACQ) effect, resulting in a decline in fluorescence over time and impacting the reliability of long-term observations, [65]. (ii) thepotential for background fluorescence or non-specific binding,leading to false-positive signals and diminished accuracy in distinguishing amyloid aggregates from other cellular proteins, [66]. (iii) a lack of specific targeting mechanisms for various stages of amyloid aggregation, particularly the highly toxic oligomers attack early aggregation stage, [67]. (iv) possible toxicity, especially athigher concentrations or with prolonged exposure, limiting their(pre)clinical or physiological applications, [68]. and (v) challenges in penetrating the blood-brain barrier and cellular membranes,as well as poor aqueous solubility [69]. These limitations severely hinder their applications for amyloid detection and imaging in in vitro and in vivo cellular environments [70]. The researcher put forth a new hypothesis and subsequently discovered an aggregation-induced emission (AIE) molecule of ROF2, which exhibits multiple functionalities as an amyloid probe and a screening tool for amyloid inhibitors (as illustrated in Figure 3a). ROF2 is a novel AIE molecule that was inspired by its ACQ counterparts, ROF1 [71]. The selection ofROF2 is mainly attributed to its (i) long wavelength emission of orange-to-red fluorescence, offering the advantage of minimiz-ing tissue auto-fluorescence during detection; (ii) easy sourcing through a one-pot synthesis, enhancing its accessibility and po-tential for widespread applications; (iii) cell membrane perme-ability for lipid droplet imaging, suggesting the potential to sur-

pass the blood-brain barrier (BBB) for advanced imaging in neu-rological studies; and (iv) limited prior exploration, with only onereported research paper available. In contrast to a ThT probe foramyloid detection, which lacks a fluorescence switching on-off mechanism and requires the use of high concentrations, ROF2not only demonstrated its enhanced sensing capability by emit-ting fluorescence upon binding to three distinct amyloid peptides— Aβ, hIAPP, and hCT (Figure 3b,c) but also effectively discrim-inated between various amyloid aggregates at different aggrega-tion stages, manifesting distinct fluorescence intensities. Further competitive binding tests involving ThT, ROF2, and amyloid pep-tides showed that ROF2 outperformed ThT in terms of superiorsensing performance, characterized by high emission intensity,rapid detection time, and heightened sensitivity, particularly evi-dent in its efficacy against the early stage amyloid species. Moreimportantly, we proposed a novel strategy, suggesting the utiliza-tion of ROF2 as a signature molecule for screening effective amy-loid inhibitors based on the following hypothesis. In the presenceof ROF2, an amyloid inhibitor candidate, and amyloid peptides, the inhibitory efficacy of the amyloid inhibitor candidate on amy-loid aggregation is reflected by the absence of direct AIE-induced fluorescence by ROF2, leading to fluorescence quenching. Conversely, unchanged AIE-induced fluorescence indicates a limitedor poor inhibitory effect of the amyloid inhibitor candidates on amyloid formation. In line with this hypothesis, employing ROF2as a screening molecule for experimental screening of potential amyloid inhibitors from 30 FDA-approved cardiovascular (CVD)drugs spanning the years 2006 to 2023 successfully identified several of these drugs as effective amyloid inhibitors (Figure 3d). Specifically, Ali5 demonstrated a strong inhibitory effect on Aβaggregation, while Tic11, Amb3, and Ang27 exhibited notable in-hibitory capabilities on hCT aggregation. However, none of these cardiovascular drugs displayed a significant inhibitory effect on hIAPP aggregation. Ali5 and Tic11 further showcased their in-hibitory properties by effectively reducing amyloid-induced cyto-toxicity in both neuronal cell models and a worm model. This study introduces a novel strategy, achieving a dual purpose by integrating the development or discovery of amyloid inhibitors through sensing molecules. The rationale for this integration lies in the common foundation shared by both the “inhibition”and “detection” of amyloid aggregates, rooted in molecular inter-actions between amyloid peptides and specific molecules [72].

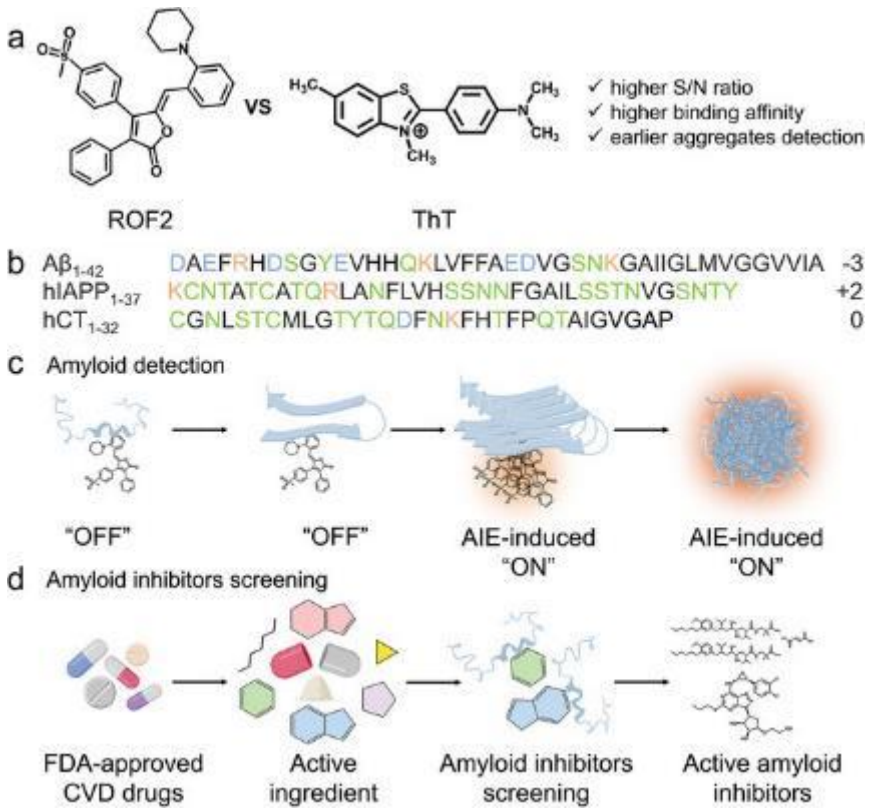

Figure 3 Dual-functional ROF2 fluorescence for amyloid detection and amyloid inhibitor screening. Chemical structure of a) ROF2 and ThT. b) Aβ, hIAPP, and hCT sequences, with color codes for positively charged residues (orange letters), negatively charged residues (blue letters), polar residues (green), and non-polar residues (black). c) ROF2 serves as an amyloid probe with an “off-on” switch for the detection of amyloid aggregates. d) ROF2 functions as a screening molecule for amyloid inhibitors, aiming to discover potential amyloid inhibitors. Adopted from ref [72].

2.3. Inhibitions of amyloid beta oligomer by nanoparticles.

Recent great advancements in nanoscience have demonstrated that nanomaterials (NMs) have the potential to serve as an ideal platform for reversing peptide aggregation due to their ability to offer a versatile design space that can effectively tackle every key link in the aggregation process. For example, graphene oxide (GO)-based nanosheets, due to their high hydro phobicity, can disrupt peptide side chains to form a highly ordered hydrophobic core during the aggregation process [73,74]. Furthermore, due to their high near-infrared-ray (NIR) photothermal conversion property, GO nano sheets can disassemble their surface-attached mature Aβ ffbers through thermal disruption [75]. Despite these desired effects, these nanomaterials suffer from several disadvantages. The hydrophobic nature of GO nano sheets results in relatively poor water dispersibility, which can provoke acute cell membrane toxicity and other bio toxicities [76]. Yin et al found that ultrasmall C3N nanodots inhibit Aβ peptide aggregation, alleviate neuron cytotoxicity, prevent neurite damage, and reduce global cerebral Aβ levels, particularly in plaques, restoring synaptic loss and ameliorating behavioral deffcits in male APP/PS1 double transgenic AD mice [77]. Recent study show that, f-Gd@C82 NPs showed excellent cytocompatibility with various tested cell lines, including primary neurons, astrocytes, human neuroblastoma cells (shsy5y), and human umbilical vein endothelial cells (HUVECs). Strikingly, the successful implementation of hydrophilic f-Gd@ C82 NPs overcomes the disadvantages of many other nano inhibitors, in terms of relieving the neuronal cytotoxicity in AD via the introduction of as many disorders as possible to inhibit/reverse Aβ aggregation without any external stimulus, thus offering a feasible route for the rational design of AD prevention and remedy strategies based on NMs [78].Typically, engineered antifibrillization nanoparticles require complex, multistep synthesis processes, such as esterification and cycloaddition, which can result in lower peptide modification efficiency. To enhance efficiency, simplify reaction conditions, and incorporate diagnostic functionality, a self-assembled fluorescent nanoparticle was designed. By synthesizing a copolymer of carboxybetaine methacrylate (CBMA) and glycidyl methacrylate (GMA), termed p(CBMA-GMA) (pCG), the hydrophilic CBMA can assemble with hydrophobic peptides to form nanoparticles, while GMA's epoxy groups can react efficiently with peptide sulfhydryl groups via click chemistry. By sequentially adding the octapeptide inhibitor Ac-LVFFARKC-NH2 (LC8) and a near-infrared fluorescent probe-peptide conjugate f-LVFFARKC-NH2 (fLC) to the pCG system, the self-assembled nanoparticle (LC8-pCG-fLC8) with Aβ inhibition and imaging capabilities was obtained (Figure 4). A series of in vitro experiments systematically investigated the imaging and inhibition capabilities of these nanoparticles, while in vivo experiments with the AD model Caenorhabditis elegans assessed the potential of LC8-pCG-fLC8 nanoparticles as an AD theranostic agent [79].

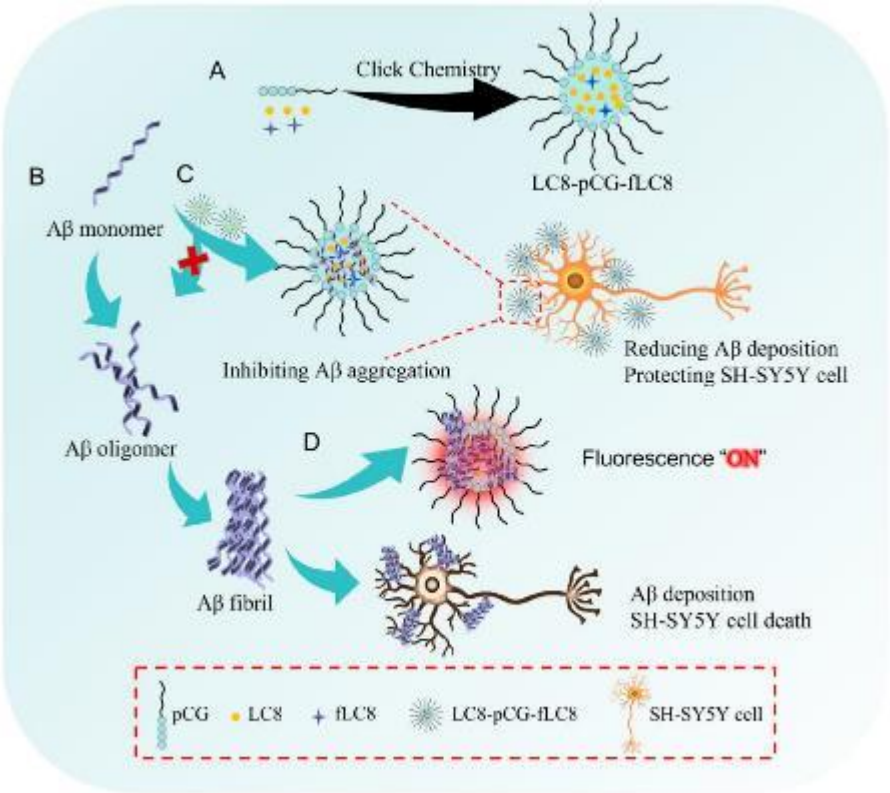

Figure 4 Schematic representation of the synthesis of LC8-pCG-fLC8 nanoparticles for Aβ inhibition and imaging. (A) Construction of LC8-pCG-fLC8 nanoparticles through a click chemistry reaction. (B) Aβ monomers aggregate into oligomers and insoluble fibrils, causing damage to neurons. (C) LC8-pCG-fLC8 modulates the on-pathway Aβ

aggregation, promoting neuron survival and exerting cell-protective effects. (D) LC8-pCG-fLC8 specifically binds to Aβ aggregates and displays an enhanced fluorescence signal, enabling early fluorescence detection of Aβ. Adopted from ref [79].

A recent study highlighted a biomass-based AIEgen derived from CS and HA, containing numerous carbonyl, hydroxyl, and amide groups. This compound effectively detects a wide range of Aβ aggregates, including oligomers and fibrils. Initially, CS and HA self-assemble into CS–HA nanoparticles through electrostatic interactions, followed by glutaraldehyde cross-linking via an efficient amino–aldehyde reaction. The resulting glutaraldehyde-cross-linked CS–HA nanoparticles (CHG NPs) feature numerous Schiff base structures and pyridine rings, [80]. and electron-rich atoms (N, O), which possess a high degree of potential to exhibit intrinsic red emission and AIE characteristics due to the presence of electrostatic interactions that play an important role in regulating Aβ aggregation, thereby leading to a better understanding of the underlying mechanisms involved in this process, [81]. Previously, our group has demonstrated the re-markable inhibitory effects of self-assembled CS–HA nano-particles with high positive charges on Aβ aggregation [82]. Therefore, it is anticipated that CHG NPs will combine the ability to probe for Aβ and potency in preventing fib-rillogenesis, rendering them a suitable option for serving as a theranostic agent that targets Aβ. [83]. beside this some nano medicine have paid attention due to nanomaterials' great bio-compatibility [84]. stable physio-chemical properties [85]. photo-luminescence properties [86]. and low cyto-toxicity [87]. Recent studies have exhibited promising results with regard to the probability of using carbon nanomaterials for amyloid fibrillogenesis [88]. The binding of graphene oxide to Aβ is facilitated by its conjugated structure, which enables hydro-phobic interactions and π-π packing interactions. For instance, thioflavin-S-modified graphene oxide under infrared laser irradiation could dissociate amyloid aggregation due to its high near-infrared absorbance, indicating the possibility of the photo-thermal treatment of AD [89]. Beyond the graphene oxide, a nano-chaperone based on a mixed-shell polymeric micelle was applicable in selectively capturing Aβ peptides, thus inhibiting Aβ aggregation [90]. Undoubtedly, one of the most difficult tasks is to identify an efficient inhibitor for fibrillation. Unfortunately, there is a lack of clarity regarding the forces that need to be engaged and the nanomolecular species that are most suitable for this purpose. In a new development in this field, we report the strong inhibition of Ab fibrillation by TGA (thioglycolic acid)-stabilized CdTe NPs. These NPs were chosen because they closely resemble proteins in terms of size, charge, and association behavior [91]. We hypothesized that a minor fraction of nanoparticles (NPs) would have the suitable local geometry and conformation of stabilizers to specifically interact with misfolded peptides, thereby either accelerating or hindering fibrillo-genesis. However, the actual NP-peptide interaction mechanism differed significantly from our expectations and previous considerations for any type of NPs. To examine the impact of CdTe NPs on amyloid-β peptides (Ab1-40) fibril formation, solutions of Ab1-40 with and without NPs were incubated. The kinetics of fibril formation were monitored using a dye-binding assay with thioflavin T (ThT), which exhibits changes in its fluo-rescent spectrum as fibrils grow [92]. CdTe NPs proved substantially more effective in in-hibiting Ab1-40 fib-rillation than small molecules and short-peptide inhibitors, requiring aggregate two to three orders of magnitude smaller than the peptide. Conversely, preventing fibrillation with small molecules and short-peptide inhibitors generally demands equal or greater amounts [93,94,95]. Recently, nanomaterials (NMs) (e.g., graphene oxide [96]. fullerenes [97]. quantum dots [98]. carbon nanotube [99]. and g-C3N4 [100,101]. Reports suggest that nanomaterials (NMs) can either directly or indirectly hinder the formation of Aβ peptide aggregates. This can encompass both the prevention of oligomer fibrillization as well as the disintegration of mature fibers in vitro. The effectiveness of NMs in inhibiting aggregation is directly connected to their physical and chemical properties, including their size, curvature, and modifications [102]. Only a small number of them have the ability to function effectively within living organisms. Notably, graphene quantum dots have been shown to prevent the formation of α-synuclein aggregates, dissolve mature fibrils, and traverse the blood-brain barrier, ultimately safeguarding dopamine neurons [103]. Research indicates that C3N nanodots can effectively prevent the aggregation of Aβ peptides and break down existing Aβ fibres, as well as alleviate the toxicity caused by these aggregates and rescue neurons from death. Additionally, they can safeguard neuron structures from damage and exhibit minimal toxicity in both laboratory and animal experiments. Notably, administering C3N nanodots intraperitoneally for six months led to enhanced learning and spatial memory abilities in double transgenic AD mice with the APP/PS1 gene [104]. Without C3N nanodots, Aβ42 peptides tend to aggregate into mature amyloid fibers, as evidenced by several experimental techniques. This includes the use of ThT fluorescence, dot blot assay, atomic force microscope (AFM), transmission electron microscope (TEM), and CD spectroscopy. Throughout these investigations, C3N nanodots have consistently demonstrated their ability to hinder the aggregation of Aβ42 peptides [105].

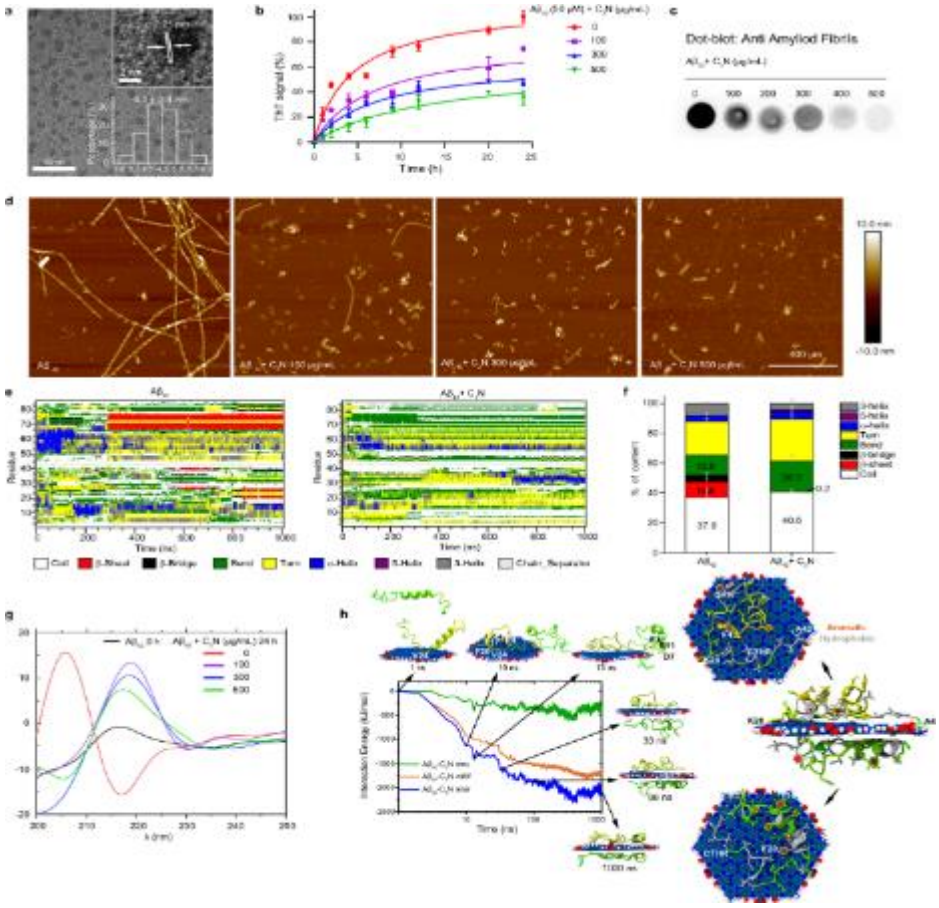

Figure 5 (a) The image in the top right corner, which is a TEM (transmission electron microscopy) image, showcases the crystal structure of C3N nanodots, along with a lateral size distribution histogram at the bottom right corner. The depict image is a representation of three separate experiments. (b) The effect of C3N nanodots on Aβ42 peptide aggregation was assessed using ThT fluorescence, and the results were expressed as the mean ± SD, with n = 3 biological replicates. The signals were normalized by setting the maximum ThT signal to 100%. (c)The formation of amyloid fibers under various conditions was evaluated using a dot blot assay and an antibody specific to Aβ fibrils conformation (mOC87) at a time of 24 hours. The immunoblots shown are from one of the three independent experiments that yielded similar results. (d) Representative AFM images of Aβ peptides, with and without treatment with C3N nanodots at concentrations of 0, 100, 300, and 500 μg/mL for 24 h, were obtained from three independent experiments. (E) The evolution over time of the secondary structure of each amino acid residue in two Aβ42 peptides was determined using the DSSP definition72. (f) The portions of each structural component in the peptides. (g)Spectral data for Aβ peptides were collected at 0 and 24 h in the absence of C3N nanodots and after a 24 h incubation with C3N nanodots.. (h) The energy produced by interactions between C3N nanodots and peptides, comprising electrostatic and van der Waals interactions, and the presence of hydrogen bonds, is depicted in this illustration. The green dashed lines represent hydrogen bonds, while hydrophobic and hydrophilic (polar/charged) residues are indicated by silver and green, respectively. Adopted from reference [104]. Carbon quantum dots (C-QDs) have garnered significant attention in the realm of bio-applications, thanks to their distinctive properties, such as biocompatibility and a plethora of functionalities [106,107]. vivo imaging [108]. , and biosensing [109]. By using the PLA method, ultra-small C-QDs with uniform morphology have been created. The experimental results from ThT fluorescence and TEM have demonstrated that C-QDs are effective in inhibiting the aggregation of Aβ42 [110]. Carbon dots, also known as CDots, were initially discovered un-intentionally during the purification of carbon nanotubes and have more recently emerged as a non toxic zero dimensional nano-material. In addition to C-QDs, C-Dots have become a popular and wild choice [111]. C-Dots were utilized as a potential drug candidate for the development of novel BBB-permeable nanomaterials for Alzheimer's disease (AD) treatment for the first time. It was anticipated that low-dimensional nanomaterials, characterised by their substantial surface-to-volume ratios, would hinder the partially unfolded Aβ by increasing the steric obstacles resulting from their interaction with Aβ monomers. the synthesized C-Dots were found to inhibit the active site of the β-secretase 1 (BACE1) enzyme and reduce the toxicity of Aβ fibrils in vitro, as well as exhibiting a potential therapeutic effect in Alzheimer's disease. Moreover, combined with previous results, it was further demonstrated that C-Dots exhibited a higher binding affinity towards the forebrain in a zebrafish model. These findings indicate the excellent potential of C-

Dots for further optimization as an antiamyloidogenic agent for AD treatment [112].Research demonstrates that Graphene quantum dots (GQDs) are composed of single or few layers of graphene with a tiny size of less than 100 nm. Their photoluminescence properties, edge effect, low cytotoxicity, and great biocompatibility have made them widely used in various fields of biological research, especially in the area of nanobiomedicine [113]. The Graphene Quantum Dots (GQDs) demonstrate a remarkable ability to effectively prevent the formation of Aβ peptide aggregates. Moreover, they have been shown to alleviate the toxic effects of Aβ oligomers. Taking these advantages into account, GQDs could be considered as promising candidates for inhibiting Aβ peptide formation or developing a treatment for Alzheimer's disease [114].

3. Conclusion

Alzheimer's disease is heavily influenced by the accumulation of amyloid-β peptides, particularly in the form of toxic oligomers. The intricate processes surrounding the formation of amyloid beta aggregates and the difficulties in detecting them at an early stage are well documented. Fortunately, the use of nanoparticles presents a promising approach for preventing and breaking down amyloid beta oligomers and fibrils, opening up a potential avenue for therapeutic intervention. Nanoparticles like graphene oxide, Graphene quantum dots (GQDs), carbon nanotube, C-Dots, fullerenes, quantum dots, C3N nanodots, and g-C3N4, f-Gd@C82, and some other nanoparticles appear to hold promise for tackling peptide aggregation in Alzheimer's disease. Some of these nanoparticles can aslo disaggregate the existing Aβ Peptide, These materials seem to be able to hinder and even reverse the aggregation of amyloid-beta (Aβ), decrease neuron toxicity, and bolster cognitive functions in animal models. However, there are still challenges to overcome, such as ensuring biocompatibility, addressing toxicity, and navigating the complexities of the synthesis process. Further research is needed to optimize these nanomaterials for safe inhibition and dis-aggregation of amyloid-beta oligomer and peptide.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors confirm that they have no conflicting interests with the contents of the manuscript.

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