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REVIEW

Recent advances in the design and applications of amyloid-β peptide aggregation inhibitors for Alzheimer's disease therapy

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Abstract

Alzheimer's disease (AD) is an irreversible neurological disorder that progresses gradually and can cause severe cognitive and behavioral impairments. This disease is currently considered a social and economic incurable issue due to its complicated and multifactorial characteristics. Despite decades of extensive research, we still lack definitive AD diagnostic and effective therapeutic tools. Consequently, one of the most challenging subjects in modern medicine is the need for the development of new strategies for the treatment of AD. A large body of evidence indicates that amyloid-β (Aβ) peptide fibrillation plays a key role in the onset and progression of AD. Recent studies have reported that amyloid hypothesis–based treatments can be developed as a new approach to overcome the limitations and challenges associated with conventional AD therapeutics. In this review, we will provide a comprehensive view of the challenges in AD therapy and pathophysiology. We also discuss currently known compounds that can inhibit amyloid-β (Aβ) aggregation and their potential role in advancing current AD treatments. We have specifically focused on Aβ aggregation inhibitors including metal chelators, nanostructures, organic molecules, peptides (or peptide mimics), and antibodies. To date, these molecules have been the subject of numerous in vitro and in vivo assays as well as molecular dynamics simulations to explore their mechanism of action and the fundamental structural groups involved in Aβ aggregation. Ultimately, the aim of these studies (and current review) is to achieve a rational design for effective therapeutic agents for AD treatment and diagnostics.

Keywords Neurodegenerative diseases · Amyloid-β fibrillation · Metal chelators · Nanotechnology · Peptide inhibitors · Computational methods

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Introduction

Alzheimer disease (AD) is the most common neurodegenerative condition and behavioral impairment, which in 1907, Alois Alzheimer first diagnosed AD in a German woman (Graeber et al. 1997). AD is considered an age-dependent disease affecting people of 65, 80, and 90 years of age with approximately 5%, 20%, and 33% levels of incidence respectively (Hajipour et al. 2017). Based on data from the Center for Disease Control and Prevention in the USA, AD is the fifth greatest cause of mortality for those aged 65 years and older. While deaths from stroke, human immunodeficiency virus (HIV), and heart disease have reduced in number over the 2000–2013 period by 23%, 40%, and 14%, respectively, deaths from AD increased by 71% over the same period. In 2015, the prevalence of AD was estimated around 46.8 million people worldwide, from which 43% need a high level of care (such as a home nurse) with an estimated caring burden of

about 236 billion dollars for people age ≥ 65 years with dementia (Alzheimer's Association 2016). It is expected that this number will surge to more than 131.5 million people worldwide by 2050 (Prince et al. 2016).

In the early stages of the disease, AD is diagnosed with an impairment in short-term memory, which gradually progresses and presents as other neurological changes and behavioral disorders (McKhann et al. 1984, Ahmad Fazili et al., 2015). The elderly population is growing worldwide, and there is currently no cure for AD. Medical advances are urgently required for the early diagnosis, prevention, and treatment for AD.

AD is likely to become one of the major healthcare and economic challenges in the world in an early future (Sloane et al. 2002; Wimo et al. 2013). The limited success of nearly all therapeutic agents on the course of the development AD has created great concern for researchers. This has led to the search for improved diagnostic and therapeutic agents to overcome such obstacles.

Pathophysiology

Death of neurons and synaptic damages the brain regions including the hippocampus, cortex, and ventral striatum which are the main neuropathological properties of AD. This pathology is responsible for brain atrophy and subsequent display of the cognitive symptoms of AD (Selkoe 2001). Brain atrophy associated with narrowed gyri, enlarged ventricles, and sulci can be observed in radiological tests of AD-affected brains (Rossor et al. 2000). However, these hallmarks are not specific to AD and may be detected in other dementia disorders. Nevertheless, the extracellular amyloid plaques, intracellular neurofibrillary tangles (NFTs), and vascular amyloid deposits are likely to reveal on postmortem AD brain at histological examination (Jaruszewski et al. 2012). In particular, extracellular amyloid-β plaques, formed by amyloid-β peptide (Aβ) aggregation, can be a unique histopathologic feature of this disease (Mandelkow and Mandelkow 1998).

The many risk factors involved in AD pathogenesis can be classified into two major categories, genetic and nongenetic. Both genetic and nongenetic factors play a major role in the causation and progression of AD. It is estimated that approximately 1% or less of Alzheimer's cases are reported because of the mutation in three specific genes (Bekris et al. 2010). These mutations influence the gene encoding the amyloid precursor protein (APP) on chromosome 21, and the gene encoding presenilin 1 (PS-1) protein on chromosome 14 and the gene encoding presenilin 2 (PS-2) protein on the chromosome (Sahni et al. 2011). Mutations in these genes lead to familial forms of AD.

People with Down syndrome are at high risk of AD. This is likely due to those with Down syndrome possessing an additional full or partial copy of chromosome 21 which contains the gene that encodes APP (Lott and Dierssen 2010). The APOE-e4 allele type is another genetic factor correlating with AD. Factors such as age, family history, diabetes, obesity, smoking, cardiovascular disease, and education have been described as the nongenetic abnormalities. The apolipoprotein E protein (ApoE) transports triglycerides, lipoproteins, and phospholipids in blood circulation and are also believed to play a key role in nerve regeneration and synaptic remodeling (Ignatius et al. 1986). The ApoE gene on chromosome 19 in humans has three major isoforms E2, E3, and E4 (Emi et al. 1988). People with the Apo ε4 polymorphism of ApoE gene are at higher risk and typically present with an earlier start of AD disease than those without the ε4 allele (Corder et al. 1993). APOE4 can behave like a pathological chaperone for Aβ peptide and can both significantly enhance Aβ deposition and diminish clearance of Aβ. However, the small ε2 allele may be protective against AD (Corder et al. 1994).

In general, two main hypotheses have been proposed to describe the etiology and pathophysiology observed in AD. The first, known as the amyloid cascade hypothesis, depends on an amyloid cascade that stimulates neurofibrillary tangle formation, with both playing a prominent role in the neurodegeneration processes. According to this hypothesis, AD advances via enzymatic cleavage of APP leading to overproduction, clearance failure, aggregation, and ultimately fibrillation of amyloid-β peptide (Aβ) with amyloid plaque formation. These conditions are related to inflammation and cell death, which is reflected in memory damage and behavioral impairment (Fig. 1) (Hardy and Selkoe 2002; Finder and Glockshuber 2007).

Mutation in APP and presenilin (PS) genes leads to an increase in Aβ senile plaques in these patients (Mattson 2004). Therefore, according to the proposed mechanism, probably, Aβ deposition can be the first pathological event that occurs years before the appearance of clinical symptoms in the brain. The intracellular neurofibrillary tangles are the driving forces in the progression towards detectable clinical symptoms (Knopman 2016; Reiman 2016).

The Aβ protein is produced in the brain and the peripheral tissues. APP is a large single-transmembrane glycoprotein that includes a large extracellular domain (590–680 amino acids) and cytoplasmic end of 55 amino acids which plays a role in intracellular trafficking. When the APP is cleaved through proteolytic processing by enzymes of β- and γ-secretases, respectively, a 39–42 amino acid protein fragment is derived from APP cleavage position (Haass and Selkoe 1993). Aβ40 accounts for approximately 90% from total formed Aβ peptide while $Aβ_{42}$ approximately 10%. It has been reported that Aβ levels in the brain tissue, CSF, and plasma of a healthy individual are in equilibrium reflecting this 90:10 ratio, which is disturbed during AD progression (Fig. 2).

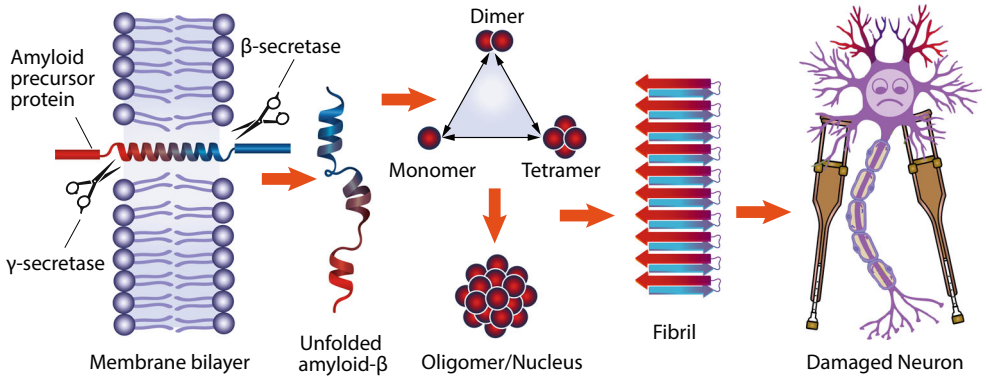

Fig. 1 The pathway of amyloid-β fibrillation formation and cellular damage. Amyloid precursor protein (APP) is cleaved by proteolytic enzymes of β- and γ-secretases, respectively, and a 39–42 amino acid peptide fragment is produced regarding with cleavage position. Unfolded Aβ monomers self-assembly into soluble toxic oligomers and insoluble fibrils lead to neural death, synaptic dysfunction, and memory impairment

In addition, it is believed that the blood-brain barrier (BBB) can help to regulate Aβ levels in the plasma and brain through the action of the receptor for advanced glycation end products (RAGE) and low-density lipoprotein receptor–related protein 1 (LRP1) receptor. LRP1 transports Aβ proteins in the abluminal and luminal direction respectively (Deane et al. 2003; Giedraitis et al. 2007; Deane et al. 2009). Aβ proteins in the brain parenchyma may form into fibrils or be degraded via various protease enzymes such as insulin-degrading enzyme (IDE), neprilysin (NEP), and angiotensin-converting enzyme (ACE).

In the AD brain, plaques can be made from several different peptides, but their cores are composed primarily of amyloid-β peptides. Due to the existence of two hydrophobic residues in the C-terminal of $Aβ_{42}$ rather than $Aβ_{40}$, Aβ shows a higher tendency to misfolding and self-aggregation as well as more cell cytotoxicity than $Aβ_{40}$ protein. For this reason, $Aβ_{42}$ peptide forms the prominent segment of neuritic plaques in AD brain, while $Aβ_{40}$ peptide is later deposited (Wisniewski and Wegiel 1995). The concentrations of both of these peptides are decreased in CSF assays of AD patients providing indirect confirmation of the presence of amyloid plaque formation (Tamaoka et al. 1997). The Aβ peptides have various aggregation forms including low molecular weight oligomers, protofibrils, and mature fibrils that eventually come together as parenchymal plaques or cerebrovascular

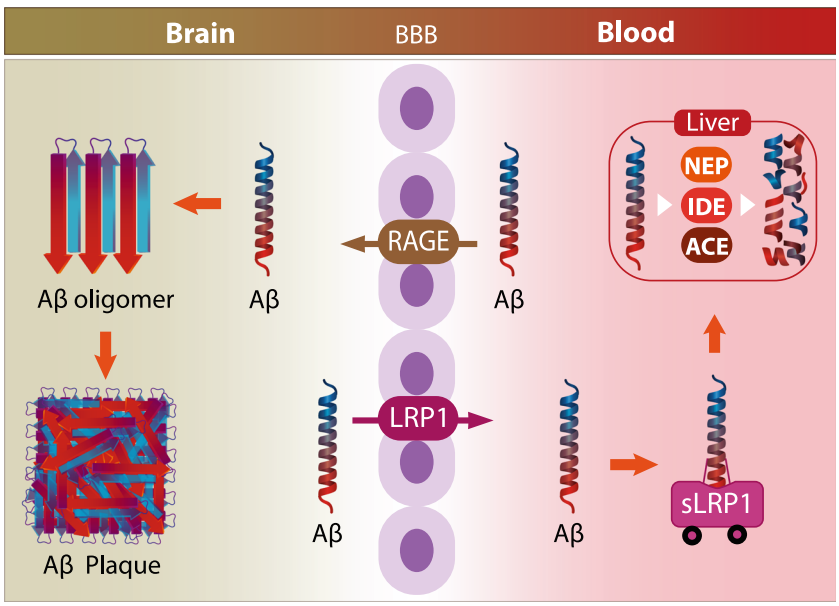

Fig. 2 The distribution and degradation pathway of Aβ peptide monomer between brain and blood circulation. BBB can regulate Aβ levels in the plasma and brain parts through the receptor for advanced glycation end products (RAGE) and low-density lipoprotein receptor-related protein 1 (LRP1) receptor that transports Aβ proteins to abluminal and luminal directions, respectively. Aβ proteins in the brain parenchyma may come together as amyloid plaques in cerebrovascular and parenchymal parts or degraded via various protease enzymes such as insulin-degrading enzyme (IDE), neprilysin (NEP), and angiotensin-converting enzyme (ACE) in liver

amyloid deposits. Recent research indicates that soluble low molecular weight Aβ aggregates are more toxic to neurons and the BBB endothelial cells and are correlated with greater loss of cognitive function than the insoluble amyloid plaque burden (Glabe 2005; Walsh and Selkoe 2007; Hall and Edskes 2009; Hall and Edskes 2012).

Tau protein is a neuronal protein, mostly expressed in axons of neuronal cells; binds to microtubules; and improves their stability. The hyperphosphorylated (P-tau) form is one of the main components in Alzheimer's neurofibrillary tangles. It is reported that P-tau cannot effectively interact with microtubules, leading to cellular dysfunction and death. It is also reported that Ptau levels in cerebrospinal fluid (CSF) raise are not only elevated in AD but also in other neurodegenerative disorders such as Creutzfeldt–Jakob, depression, and Parkinson's disease. Therefore, neurofibrillary tangles are not specific to AD, and because of their location inside cells, their presence is difficult to be directly compared with production and aggregation of the Aβ peptide (Larbanoix et al. 2011).

The second hypothesis concerns the cholinergic system deficiency. Based on the hypothesis of the cholinergic pathway, the cholinergic neurons dysfunction is adequate to create animal models with a memory impairment similar to AD (Bartus and Emerich 1999). The obtained results of Rossor et al. (1980) and Henke and Lang (1983) studies demonstrated that there is a marked degeneration in cholinergic neurons and cholinergic markers in the brains of AD patients. Additionally, both AChE levels and choline acetyltransferase (ChAT) efficacy were decreased in the cortex of AD patients (Rossor et al. 1980; Henke and Lang 1983).

In another study, Soininen et al. (1995) reported AD patients possessing the APOE-ε4 allele to have a severe defect in cholinergic systems in comparison with those of without the APOE-ε4 allele. An effective cure for AD is not yet a reality, and approved drugs for treatment of the cognitive and behavioral impairments in AD are based on neurotransmitter or enzyme modulation that can only improve symptoms (Sood et al. 2014). Acetylcholinesterase (AChE) inhibitors such as tacrine, donepezil, rivastigmine, and galantamine are currently being utilized to reduce the rate of AD progression (Han et al. 2015).

Due to their unfavorable pharmacokinetics and pharmacodynamics properties, there are several limitations associated with therapy such as dizziness, confusion, and adverse gastrointestinal effects (such as nausea, constipation, and vomiting) that most usually result in the defeat of therapy (Mehta et al. 2012; Colovic et al. 2013). In recent years, a significant volume of research has been focused on achieving a better understanding of AD pathogenesis and development of a new class of therapeutic strategies that could stop disease progress by targeting special pathophysiological mechanisms in the AD process.

Amyloid hypothesis summary Although the pathogenesis of AD is not yet entirely understood, among the reported biological pathways, the amyloid cascade hypothesis has developed as the dominant theory to explain the etiology and the fundamental focus on neurodegenerative studies. As a consequence, many scientists are currently investigating therapeutic strategies targeting the molecular mechanisms of the processes of production, aggregation, and clearance of Aβ. Based on this hypothesis, Aβ monomers self-assemble into soluble toxic oligomers and insoluble fibrils, leading to neural death, synaptic dysfunction, and memory impairment. Although Aβ hypothesis-related therapy strategies are more developed than other strategies, there have been to date no demonstrated clinical benefits by them.

It is believed that low molecular weight oligomers of Aβ proteins can be more toxic to neurons and BBB endothelial cells than the monomers or large fibrils (Hall and Edskes 2009; Laganowsky et al. 2012). Therefore, there are strategies to prevent or reduce Aβ aggregation that include either metal chelators or β-sheet breakers based on nanotechnology, organic molecules, or peptides/antibodies (Figs. 3 and 4).

Different strategies for Aβ fibrillation inhibition have been designed and proposed in vitro, but experimental investigations alone are not adequate for having a clear understanding of the subject. Also, the mechanism of molecular interaction between inhibitors and the Aβ peptides is often unknown. Therefore, in order to improve and develop new inhibitor compounds, it is necessary that the field should acquire sufficient knowledge about interactions at the molecular and atomic levels. Moreover, computational methods, like molecular docking and molecular dynamics simulations, are an essential supplement to experimental studies and have provided novel viewpoints in many fields. Furthermore, these techniques have been widely applied for the design of Aβ aggregation inhibitors on the conformational transitions, metal chelation, and aggregation formation (Bruce et al. 2010; Lemkul and Bevan 2012; Rao et al. 2015).

Metal chelators

Metal ions have a vital role in the process of production and clearance of Aβ peptide through the regulation of the activity of enzymes involved in this process (Sastre et al. 2015). They are considered an important factor in determining neuronal function and AD progression. Although the exact mechanism of metal ion interactions with Aβ peptide is not still clear, a preponderance of evidence indicates that these ions can attach with high affinity to N-terminal residues of Aβ peptide, such as His6, His13, and His14 imidazole, as well as the Asp1 and Ala2 carbonyl groups (Schöneich and Williams 2002).

It is believed that heavy metal ions like copper, iron, manganese, zinc, and aluminum (especially copper) can

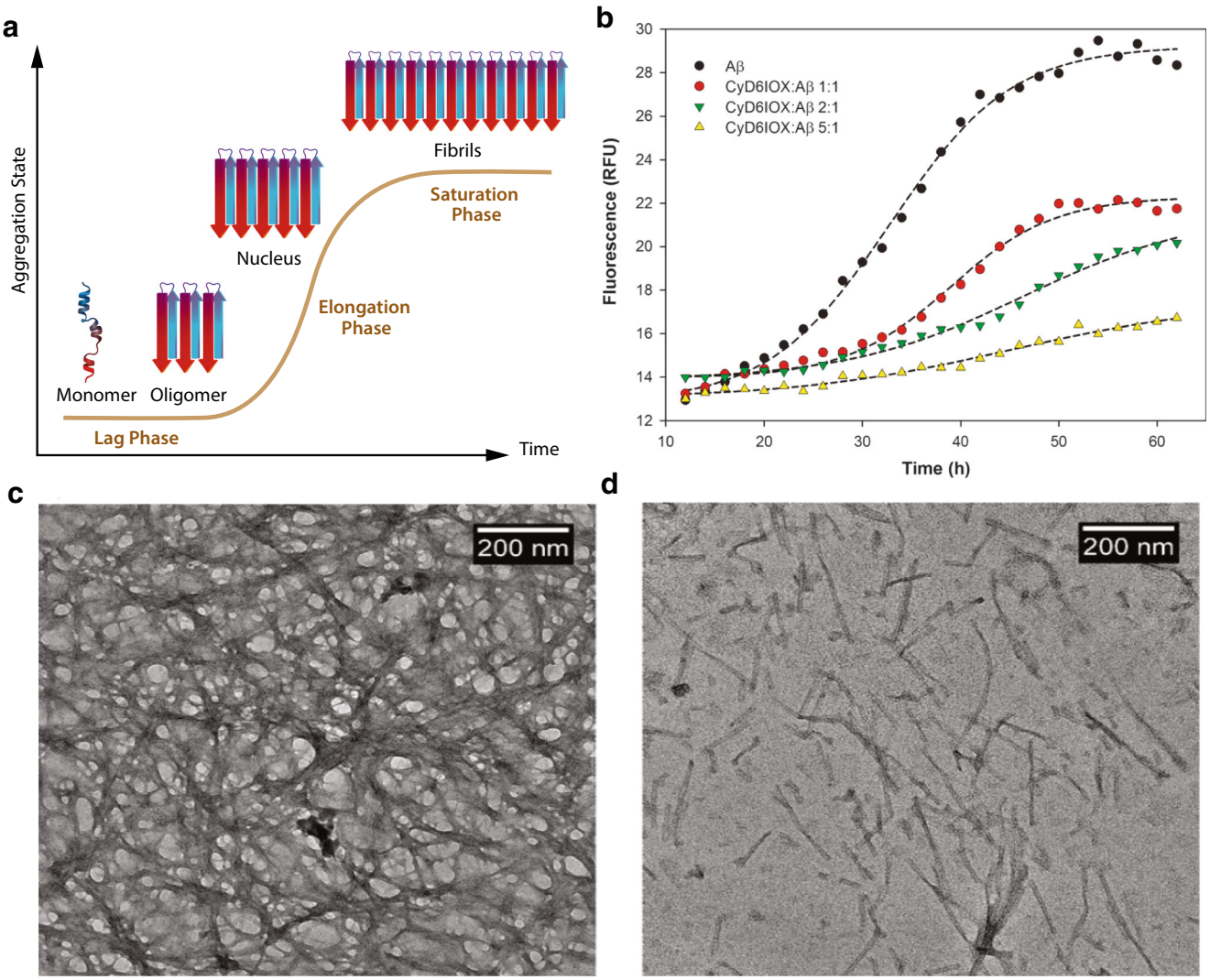

Fig. 3 Sigmoid kinetics diagram of Aβ peptide fibrillation formation including lag, elongation, and saturation phase. **a** β fibril formation is a self-assembly process which depends on nucleation, which has three phases including lag phase (critical oligomer cores formation), elongation phase (oligomers polymerization), and fibril saturation phase. **b** Kinetic profiles of $A\beta_{42}$ aggregation alone and in the presence of CyD6IOX (conjugated cyclodextrin to quinoline derivative, Oliveri et al. 2017). **c** TEM image of $A\beta_{40}$ fibrils. **d** Inhibition of $A\beta_{40}$-fibril growth in the presence SLOH (carbazole-based fluorophores, Yang et al. 2012)

stimulate both Aβ aggregation and fibril formation as well as accelerate oxidative stress by generating neurotoxic reactive oxygen species (ROS) containing oxygen free radicals and hydrogen peroxide (H_2O_2), thereby causing synaptic dysfunction (Singer et al. 2005). In addition, it was reported that Cu^{2+} ions exhibit a higher catalyzing effect at slightly acidic condition (< pH 6.8) on Aβ aggregation compared with Zn^{2+} ions at physiological pH (Atwood et al. 1998; Pedersen et al. 2015).

Chelation therapy has been suggested as a possible treatment method for AD due to its ability to absorb and reduce the concentration of available metal ions in the brain. However, their application may be associated with challenges like low CNS bioavailability and notable systemic toxicity. In addition, metal ion chelators can inhibit the interaction of Aβ peptide with the lipid membrane—a process known to influence Aβ peptide aggregation (Mandel et al. 2007).

Many metal chelators such as ethylenediaminetetraacetic acid (EDTA) (Casdorph 1981; Chauhan and Siegel 2007), diethylenetriaminepentaacetic acid (DTPA), desferrioxamine (Atwood et al. 2000; Liu et al. 2006), and clioquinol have been considered agents for inhibition of Cu^{2+}-mediated Aβ aggregation in vitro (Table 1). Among these traditional metal chelators, only a few agents, such as clioquinol (CQ) (Ritchie et al. 2003) and 25,7-dichloro-2-((dimethylamino) methyl) 8-quinolinol (PBT_2) (a 8-hydroxyquinoline derivative), have been evaluated in murine AD models and AD human patients (Adlard et al. 2008). The result revealed that they have significant inhibitor activity and they have currently passed phase II clinical trials (Crouch and Barnham 2012). However, it is

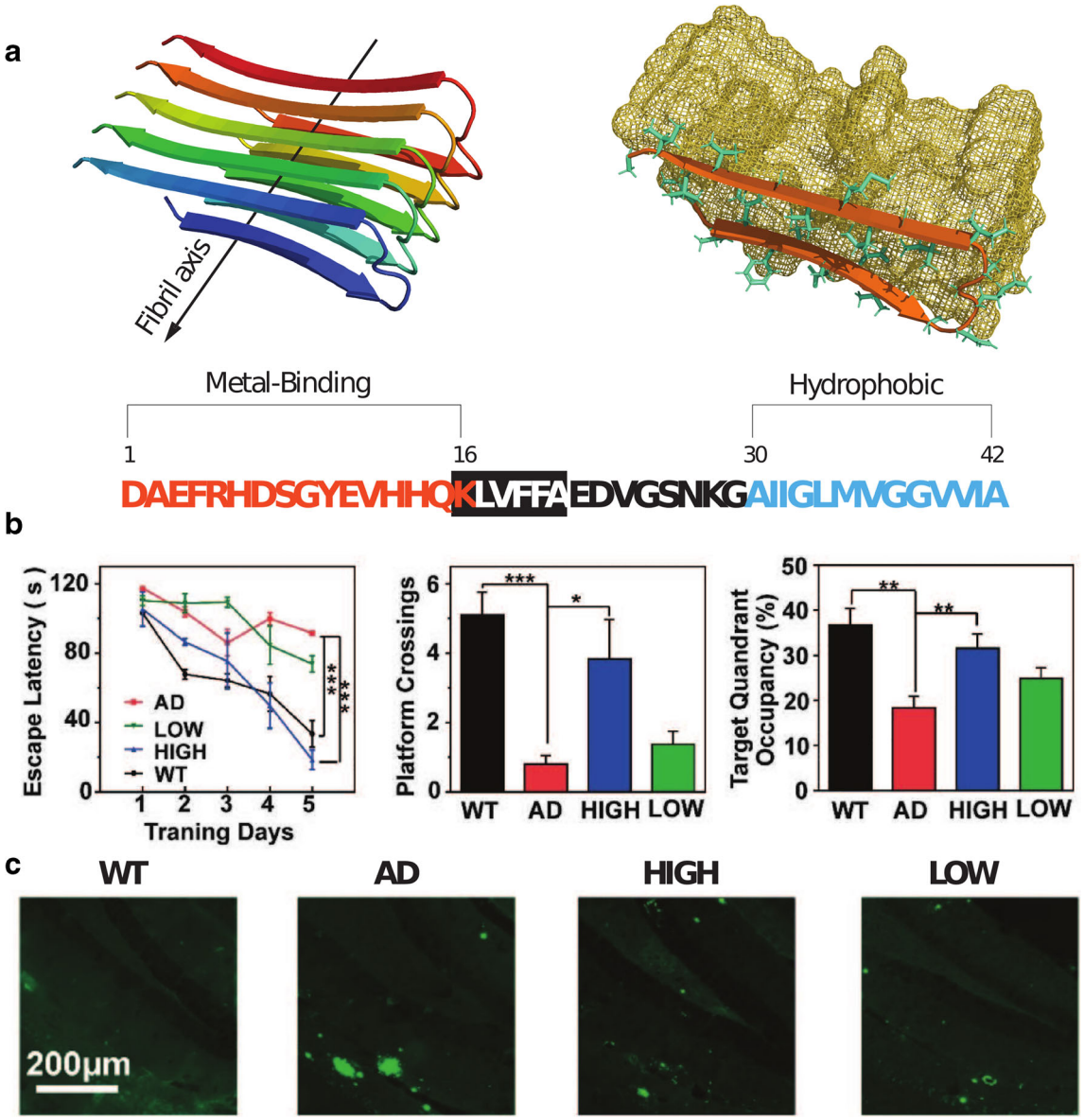

Fig. 4 **a** Schematic illustration of the structure of the Aβ fibril. **b** Behavioral test for memory impairment in AD model and treated with 1.0 mg/mL (low dose) and 1.5 mg/mL (high dose) with PtII-PW11; latency for escape to platform in the training phase, number of crossing platform time in probe test and percentage (%) of time spent in the target quadrant in probe test. **c** Immunofluorescence images for senile plaques ($A\beta_{42}$ deposition) in the hippocampus (HIP) of WT, AD, and treated with PtII-PW11 (organoplatinum-substituted polyoxometalate, Liu et al., 2019a, b, c)

likely that the potential side effects of these metal chelators may prevent their public clinical use.

Cherny et al. reported modified polymeric nanoparticles with D-penicillamine via a disulfide bond as a copper chelator (Cherny et al. 2001; Cui et al. 2005). The resulting nanoparticles displayed a good ability to disaggregate Aβ plaques in vitro. In another study, an ultra-thin structure of graphite-phase carbon nitride (g-C_3N_4) was described as a nanochelator able to prevent $A\beta_{40}$ fibrillation (Li et al. 2016). This nanostructure could specifically bind to Cu^{2+} ions, thereby inhibiting fibrillation and causing depolymerization of the deposited Aβ40 aggregates in conjugation with Cu^{2+} ions. Sun et al. attached iminodiacetic acid (IDA) to the human lysozyme (h-Lys)–coated surface of polymeric-based nanoparticles and demonstrated a strong binding affinity to Zn^{2+} ions (Liu et al. 2017a; Li et al. 2018). This nanochelator can inhibit $A\beta_{40}$ fibrillation, rapidly destabilizing Zn^{2+}-associated Aβ aggregates and modulating the resulting cytotoxicity.

In 2019, Liu and colleagues developed a potent multifunctional inhibitor of Cu^{2+}-mediated Aβ aggregation based on the D-enantiomeric RTHLVFFARK-NH_2 decapeptide a peptide sequence shown to act as a high-affinity chelator to Cu^{2+} ions (Meng et al. 2018; Liu et al. 2019b). In the same study, they showed that the D-enantiomer peptide had an inhibitory

Table 1 Metal chelator-based strategies for inhibition of Aβ peptide aggregation

Number	Structure	Metal/fibril	Model of use	Therapeutic effect/category	Ref.
1	A carboxylic acid Gemini surfactant (SDUC)	$Cu^{2+}/A\beta_{40}$	In vitro	o More ability for disaggregation of Cu^{2+}-triggered $A\beta_{40}$ fibers than EDTA	(Zhu et al. 2014)
2	Carnosine-LVFFARK-NH_2 (Car-LK7) peptide	$Cu^{2+}/A\beta_{40}$	In vitro	o Dual functionality o High inhibitor capability on Aβ aggregation and ROS generation rather than LK7	(Zhang et al., 2018a, b, c)
3	Modified LVFFARK (LK7) peptide with HH to the C-terminus	$Cu^{2+}/A\beta_{40}$	In vitro	o Dual functionality o High inhibition capability on Aβ aggregation, ROS generation and toxicity as compared with LK7 o Biocompatibility	(Zhang et al., 2018a, b, c)
4	Macrocyclic polyamines (cyclam derivatives)	Zn^{2+}, $Cu^{2+}/A\beta_{40}$	In vitro	o Significantly reduce H_2O_2 formation and neurotoxicity o High antioxidant ability Favorable BBB penetration	(Yang et al. 2015, Savelieff et al. 2018)
5	Derivatives of PDE9 inhibitors	$Cu^{2+}/A\beta_{42}$	In vitro	o Considerable metal-chelating capacity in comparison with clioquinol o Good blood-brain barrier permeability o High antioxidant activity	(Su et al. 2016)
6	5(4Nitrophenyl)diazenyl)quinolin-8-ol (HL1) and 4-((4-nitrophenyl)diazenyl)benzene-1,3-diol (HL2) (azo dye–based compounds)	Cu^{2+}/chicken egg white lysozyme (CEWL)	In vitro/DFT calculations	o Dual functionality o Excellent colorimetric sensor for amyloid fibrils	(Rana et al. 2018)
7	2,2′-Bipyridine (bpy) derivatives	Cu^{2+} and $Zn^{2+}/A\beta$	In vitro	o Dual functionality o Low cytotoxicity o BBB permeable	(Ji et al. 2017)
8	GGH peptide	$Cu^{2+}/A\beta$	In vitro	o A high decrease in the level of $HO^{\bullet}$ radicals o Good biocompatibility o High-chelating selectivity to Cu^{2+}in the presence of other metal ions (e.g., K^{+}, Ca^{2+}, Ni^{2+}, Mg^{2+}, and Zn^{2+})	(Hu et al. 2016)
9	Modified benzothiazole salicylaldehyde (SA)-based Schiff bases as the chelators	$Cu^{2+}/A\beta$	In vitro	o Dual functionality o Significant antioxidant capacity o Dissolution ability the formed fibrils o Multivalent effect o Reduce Aβ cellular toxicity	(Geng et al. 2012)
10	Clioquinol (CQ) derivatives	$Cu^{2+}/A\beta_{42}$	Molecular dynamics study	o Cl-based CQ derivative, higher disaggregation capacity in comparison with other derivatives o H-bond formation with D23 of $A\beta_{42}$ peptide	(Dong et al. 2016)
11	Pseudopeptide L, derived from nitrilotriacetic acid scaffold and functionalized with three histidine residues	$Cu^{2,1+}/A\beta$	In vitro	o Coordination with Cu (I) and Cu (II) o Prevent reactive oxygen species formation	(Conte-Daban et al. 2017)
12	Brazilin compound	$Zn^{2+}/A\beta_{42}$	In vitro	o High ability to sequester Zn^{2+} from the $A\beta_{42}$-Zn^{2+} complex o Inhibition the Zn^{2+}-mediated aggregation of $A\beta_{42}$	(Guo et al. 2017)
13	N1-(7-nitrobenzo[c][1,2,5]oxadiazol-4-yl)N2,N2-bis(pyridin-2-ylmethyl)ethane-1,2-diamine (NBD-BPEA) compound	$Cu^{2+}/A\beta_{40}$	In vitro	o Dual functionality o Inhibit the metal-mediated $A\beta_{40}$ aggregation o Disassemble performed $A\beta_{40}$ aggregates o Promotes the reversion of the β-sheet to the normal random coil conformation	(Chen et al. 2018)

Table 1 (continued)

Number	Structure	Metal/fibril	Model of use	Therapeutic effect/category	Ref.
				o Suppress the intracellular ROS and protect against cell apoptosis o Antioxidant activity	
14	Ionophoric polyphenols	$Cu^{2+}/A\beta_{40}$	In vitro	o Excellent antioxidant properties o Better scavenge DPPH (1,1-diphenyl-2-picryl-hydrazyl) and AAPH (2,2-azobis(2-amino-propane) dihydrochloride) free radicals than clioquinol, resveratrol, and ascorbic acid comparable with lack of toxicity to that of resveratrol	(Martínez et al. 2016)
15	8-Hydroxyquinoline derivatives	$A\beta_{42}$ or $Zn^{2+}/A\beta$	In vitro/in vivo	o Significant inhibitory effects against self-induced Ab aggregation o Potential antioxidant properties o Penetrate the blood-brain barrier (BBB) in vitro. Any acute toxicity in mice at doses up to 2000 mg/kg in vivo	(Yang et al. 2018)

effect on $A\beta_{40}$ fibrillogenesis and significantly decreased the cytotoxicity caused by $A\beta_{42}$-Cu^{2+} complexes in comparison to that showed by using its L-enantiomeric analog. In a similar study, the in vivo pharmacodynamics effects of a bifunctional inhibitor peptide GR (GGHRYYAAFFARR) were investigated on the basis of its dual ability to act both as a chelator of Cu ions and a β-sheet breaker able to reduce ROS toxicity and inhibit $A\beta_{40}$ fibrils, respectively (Zhang et al. 2016; Wang et al. 2018). The in vivo results indicated that the GR peptide could improve damaged spatial memory and reduce the number of senile plaques within the brain of AD model rats. Recently, in our research group, a new multifunctional peptide LPFFDGNSM for metal chelation and $A\beta_{42}$ inhibition was designed based on the iAβ5 peptide lead compound (Shamloo et al. 2018). Subsequently, its chemical inhibitory mechanism involving Zn^{2+} and Cd^{2+} ions was evaluated using MD simulation techniques. The findings indicated that these ions interact with six druggable regions with considerable affinities on the $A\beta_{42}$ peptide. According to the conducted free energy analysis, the ions showed higher affinity to the LPFFDGNSM sequence rather than the $A\beta_{42}$ peptide. In fact, the formation of the reported LPFFDGNSM-ion conjugates is easier and more spontaneous than the presented Aβ-ion^{+} ones.

β-Sheet breakers

The structure of the $A\beta_{42}$ fibril was first experimentally resolved by Lührs et al. (2005) (Fig. 4a). This structure provides important information about the identification of interacting regions, which might be targeted by inhibitor compounds (Lührs et al. 2005). There are at least four important sites with specific structural properties which either promote interaction or destabilize Aβ self-assembly: (a) hydrophilic region formed by electrostatic interaction between Asp23-Lys28; (b) Glu22 ladder formed between Glu22 residue side chains of adjacent β-sheets; (c) central cleft in the interior of the U-shaped turn; and (d) hydrophobic regions by Leu17-Ala21 and Ala30-Val36 residues of the N- and C-terminal β-strands, respectively.

The salt-bridge formed between Asp23 and Lys28 residues has a vital role in stabilizing the β-sheet conformations. It is believed that the salt-bridge can stimulate the oligomerization of Aβ by stabilizing the Val24-Asn27 turn (Reddy et al. 2009). The hydrophobic residues in the C-terminus moiety (saddle form) especially Met35 play an important role in fibril stabilization due to modulating Aβ aggregation via hydrophobic interactions. The met35 binding site is therefore considered a potential site to prevent protein–protein interactions and inhibit amyloid fibril formation (Friedemann et al. 2015). However, the central hydrophobic region (17–21) can inhibit

fibrillation formation by reducing elongation along the major fibril axis.

Overall, the central hydrophobic core (K16LVFF20), hydrophobic C-terminal residues (29–36), and turn segment are critical regions on $A\beta_{42}$ which are able to initiate nucleation, enhance conformational transition of Aβ, and promote fibril formation. Therefore, compounds with the potential to act as β-sheet breakers tend to interact with these binding regions responsible for the formation of stable β-conformation and long growth of fibrils. Also, they interfere with hydrophobic contacts within the monomeric structure required for polypeptide collapse and dense conformation by electrostatic, hydrophobic, and π–π interactions (Eskici and Gur 2013). In the following section, we classify them into three main groups, focusing on new achievements in each class separately.

Nanoparticles

Nanostructures are not employed as a carrier for transporting active agents across the BBB in the treatment of AD. Moreover, many studies have focused on designing brain-specific nanostructures capable of protecting neurons from aggregated Aβ toxicity by inhibiting Aβ fibrillation and delaying the accumulation of Aβ oligomeric species (Table 2). Such nanomaterials can directly interact with the Aβ peptides or the aggregated amyloid, thereby overcoming peptide self-assembly into fibrillar plaques or toxic oligomers. Aβ fibril formation is a nucleated self-assembly process that has three phases which include the lag phase (critical oligomer cores formation), the elongation phase (oligomers polymerization), and a pseudo equilibrium/fibril saturation phase (Fig. 3) (Gillam and MacPhee 2013). Nanotechnology-based agents can influence both the lag, elongation, and saturation phases by efficient adsorption of monomers, oligomers, and protofibrils, features enhanced by their unique properties such as large surface-to-volume ratio (Cabaleiro-Lago et al. 2008).

Kumaraswamy et al. (2012) obtained liposomes by the thin-film hydration procedure. Thermal studies revealed that β-sheet breaker agents inserted into the hydrophobic core, where it presented a lower surface tension. This characteristic enabled these liposomes to act as potential therapeutic agents for the inhibition of amyloid aggregation. In another study, Aβ proteins were inserted into amphipathic nanogels composed of cholesterol-bearing pullulan (CHP). The amphipathic properties of these CHP gels afforded them properties similar to natural chaperones (Ikeda et al. 2006). Recently, Boridy et al. (2009) indicated a great reduction in $A\beta_{42}$-associated toxicity in primary cortical and microglial cell culture after using CHP nanogels. PEGylated phospholipid nanomicelles have also been reported capable of inhibiting Aβ self-assembly (Joshi et al. 2010) by promoting the interaction between the micellar interfaces and the Aβ peptide. Podolski et al. (2007) illustrated an anti-assembly effect of C_{60} hydrated fullerene ($C_{60}H_yF_n$) on the fibrillation of $A\beta_{25–35}$ fragment. They demonstrated that injection of 3.6 nM of $C_{60}H_yF_n$ to each of the brain ventricles could prevent and improve the cognitive impairment in AD-affected rats. Kogan et al., in order to destroy amyloid aggregations, utilized local thermal energy that was generated by a mixture of gold nanoparticles (AuNPs) and weak microwave fields (Kogan et al. 2006). The AuNPs are targeted to Aβ plaques, and when enveloped in a weak microwave field, thermal energy was produced, helping to destroy the plaque. Each AuNP provided thermal energy of approximately 10–14 J/s, whereas the required energy for breaking a fibril non-covalent bond is about 10–20 J per bond per μs. It is found that gold NPs of 23 nm can be used as a probe to detect the formation of Aβ fibrils and oligomers (Elbassal et al. 2017). It is shown that this simple, low-cost AuNP-based assay is sensitive to the quantity and oligomeric structures of both $A\beta_{40}$ and the $A\beta_{40}$-K16Nle mutant.

Recent studies have exhibited that curcumin may help to delay or inhibit amyloid-beta aggregation due to neuroprotective and cognitive-enhancing properties. However, poor solubility and bioavailability of curcumin have limited its clinical applications (Anand et al. 2007). Polyvinylpyrrolidone conjugated with curcumin coated on the surfaces of gold nanoparticles (PVP–C–AuNP) can increase the bioavailability and solubility of curcumin (Brahmkhatri et al. 2018). In this study, the inhibitory effect of curcumin nanoconjugates was evaluated using TEM analysis of fibers formed from the short $A\beta_{1–16}$ fragment. It was found that this fragment promotes aggregate formation in the healthy brain. The results showed that curcumin nanoconjugates could stop $A\beta_{1–16}$ fibrillation and decompose formed aggregations (Anand et al. 2007).

NPs can show dual effects of inhibition or acceleration on the nucleation process according to their physical and chemical features such as size, shape, surface modification, charge, composition, and concentration (Cabaleiro-Lago et al. 2008; Yoo et al. 2011; Sudhakar et al. 2017; John et al. 2018). They show different binding affinity to Aβ monomers and oligomers in various conditions and are therefore also capable of having different effects on the fibrillation process. NP diameter and surface chemistry can modulate the extent of aggregation, while NP electric charge influences the aggregation morphology (Moore et al. 2017). Recently, much attention has been paid to the study of the effect of nanoparticles on the folding and aggregation of peptides.

Size effects of gold nanoparticles (AuNPs) and nanoclusters (AuNCs) stabilized with L-glutathione were reported to play a role in inhibiting protein amyloidosis (Gao et al. 2017). It is described that large AuNPs accelerate Aβ fibrillation, whereas small AuNPs significantly suppress fibrillation process. More interestingly, AuNCs with smaller sizes can completely inhibit the nucleation and amyloidosis. In another study, the effects of gold nanoparticles (AuNPs) with different shapes (nanospheres and cubes) and the same

Table 2 Nanotechnalogy-based strategies for inhibition of Aβ peptide aggregation

Number	Structure	Size in PBS (nm)	Model of use	Therapeutic effect/category	Ref.
1	Self-assembled chitosan-hyaluronic acid composite (CH) NPs	Range of 80–4-10	In vitro	o Effects of surface charges of nanoparticles on Aβ aggregation o Higher inhibitory effect of the surface charges density and positive CH than the negative one o Inhibit the conformational transitions of Aβ o Potent suppressing the nucleation and fibrillation by electrostatic interactions	(Jiang et al. 2018)
2	Poly N-isopropylacrylamide (NIPAm)/acrylic acid (AAc)/N-tbutylacrylamide (TBAm) Polymeric NPs (negatively charged hydrophobic) and (−)-epigallocatechin-3-gallate (EGCG)	74.1 ± 4.9	In vitro	o An dual-inhibitor system o Highly effective on the inhibition and detoxification of $A\beta_{42}$ at low concentrations of the inhibitor system o Function in different Ab assembling stages: polymeric NPs: inhibition of primary nucleation, EGCG suppression of fibril elongation	(Liu et al. 2016; Liu et al. 2017a, b)
3	Self-assembled nanogels of curcumin-hyaluronic acid conjugates	100–300	In vitro	o Synergistic functions of nanogels: o Higher inhibition effects than free curcumin o Protection cells from the toxicity of free curcumin interfere with the interactions between Aβ molecules	(Jiang et al. 2016)
4	Self-assembled biodegradable EGCG-Fe(III)/PVP nanoparticles	3.2	In vitro	o A dual-inhibitor system o Ultra-small size o Good biocompatibility o Synergistic inhibitory effects: by the PVP hydrophobicity on the primary nucleation and antioxidant activity of EGCG on secondary nucleation during the $A\beta_{40}$ fibrillation o Easy synthesis o High stability in simulated body fluid o High antifibrillation performances towards the of $A\beta_{40}$ and Biodegradable property	(Liu et al., 2019c)
5	Copolymeric N-isopropylacrylamide: N-tert-butylacrylamide (NiPAM:BAM) nanoparticles	40	In vitro	o The main effect on the nucleation step of Aβ fibrillation and unaffected on the elongation step	(Cabaleiro-Lago et al., 2008)
6	Amino-modified polystyrene nanoparticles	57–180	In vitro	o Inhibition of the fibrillation process at large particle surface area	(Cabaleiro-Lago et al. 2010)
7	Single-walled carbon nanotube (SWNT) surface	-	MD simulation	o Induced β-barrel formation of $A\beta_{25–35}$ oligomers o Assembling $A\beta_{25–35}$ β-sheets with antiparallel-parallel strands into β-barrels wrapping o Inhibition of β-sheet formation and the destabilization of prefibrillar β-sheets	(Fu et al. 2009, Li et al., 2011a, b)
8	Hydroxylated single-walled carbon nanotubes	-	In vitro/MD	o Inhibition $A\beta_{42}$ fibrillogenesis and disaggregates mature fibrils o Cytoprotective effects against $A\beta_{42}$ fibrillation-induced cytotoxicity o Contribution most of the free energy by binding nonpolar interactions especially van der Waals forces o Main regions in interaction H13-Q15 and V36-G38 residues o Improve inhibitory capacity and protective effect in o A high ratio of hydroxyl groups in SWNT	(Liu et al. 2018)
9	Gold and silver surfaces	-	Computational methods	o Adsorption of peptides onto gold and silver surfaces o Prone to β-sheet-rich conformations and aggregation o A new mechanism for the acceleration of fibril formation based on interaction with nanoparticles	(Soltani and Gholami 2017)
10	LVFFARK-functionalized nanoparticles(LK7@PLGA-NP-s)	161	In vitro	o Little cytotoxicity than unconjugated LK7 o Remarkable inhibitory capability against $A\beta_{42}$ aggregation and Aβ-induced toxicity at a low concentration (20 μg/mL) than free LK7	(Xiong et al. 2015)

Table 2 (continued)

Number	Structure	Size in PBS (nm)	Model of use	Therapeutic effect/category	Ref.
				o Postpone and disruption of conformation transition of Aβ o Redirection of $A\beta_{42}$ aggregation pathways	
11	Dual peptide inhibitors coupled on AuNPs-VVIACLPFFD (VCD10)@AuNP	-	In vitro	o Most effective peptide@AuNPs on inhibition and cytotoxicity of the $A\beta_{42}$ aggregation o Increase cell viability from 48 to 82% at a dosage as low as 40 nmol o Due to the branched dual-inhibitor sequence, special surface orientation, and conformation	(Xiong et al. 2017)
12	Epigallocatechin-3-gallate (EGCG)-stabilized selenium nanoparticles coated with Tet-1 peptide	-	In vitro	o Effective inhibition Aβ fibrillation and disaggregate preformed Aβ fibrils into nontoxic aggregates significantly enhance in the cellular uptake of Tet-1-EGCG@Se in cells rather than EGCG@Se o Remodeling Aβ fibrils into spherical aggregates (nontoxic and non-β-sheet structure) o Protection cells against Aβ-induced damage by suppressing the generation of ROS and DNA fragmentation	(Zhang et al. 2014)
13	Self-assembled curcumin-poly (carboxybetaine methacrylate) nanogels	120–190	In vitro	o The higher inhibitory effect on $A\beta_{42}$ fibrillation, and cytotoxicity than free curcumin due to the high hydration nature of the polymer o Suppress the conformational changes from α-helix to β-sheet-rich structures	(Zhao et al. 2018)

size on the aggregation of an $A\beta_{40}$ peptide were evaluated (Wang et al. 2019); the results demonstrated that nanospheres show a significant acceleration effect on nucleation and fibrillation process in comparison with nanocubes. This effect may be due to factors such as higher degree of the gold NP surface availability and greater affinity of nanospheres to $A\beta_{40}$. In another report, it was demonstrated that small, spherical AuNPs have higher anti-fibrillation effects than large, nanocube ones (Liao et al. 2012). In addition, negatively charged gold NPs can delay aggregation processing via more absorption of Aβ monomers rather than positively charged ones (Liao et al. 2012).

The inhibitory ability of gold nanospheres can also change with different surface coatings. PAA (polyacrylic acid)-coated NPs of 18 nm and smaller (8 nm) are superior inhibitors as they can inhibit aggregation at substoichiometric ratios as low as 1:2,000,000 with in relation to Aβ (Moore et al. 2017). Previous reports showed that small iron oxide NPs, with negative charge, presented higher inhibitory activity than their large, positively charged ones (Pansieri et al. 2018). Other investigations illustrated that negatively charged inorganic CdTe (Yoo et al. 2011) and graphene oxide (Mahmoudi et al. 2012) grab Aβ monomers and oligomers to postpone fibrillation phase, while positively self-assembled chitosan-hyaluronic acid composite (CH) NPs exhibited higher inhibitory effect than did the negatively charged ones (with regard to Aβ aggregation) (Jiang et al. 2018). The concentration of nanoparticles can be a decisive factor. Polystyrene NPs present at a high concentration present a large surface area that can capture free Aβ peptides and inhibit fibrillation, while a low concentration can play a role similar to preformed seeds that improve the fibrillation rate (Cabaleiro-Lago et al. 2010).

Organic molecules

In this section, we review the different groups of natural and synthetic small molecules which are able to block the initial stages of Aβ peptide aggregation and toxicity. They may be described as unique pharmacological agents in Alzheimer's diseases (Table 3).

A large number of small molecules such as polyphenols, inositols, organofluorines, and quinones and their derivatives were trialed and introduced as potential inhibitors of amyloid formation (Brahmachari et al. 2017). These compounds present significant antioxidant and anti-inflammatory properties and as such may play a principal role in diminishing age-dependent oxidative stress and inflammation. Thus, they can obstruct the start of neurodegenerative disorders. Second to this is that these compounds may competitively interact with aromatic amino acids such as phenylalanine in Aβ peptide and impose barriers between aromatic groups, hereby limiting the π–π interactions and preventing the self-assembly process by enhancing the stability of amyloid peptides in the native state (Ahmad et al. 2011). Third, they may inhibit toxic Aβ oligomer interaction with the cell membrane by selective neutralization of the toxic Aβ structural conformation. Also, they

may reduce Aβ production via stimulation of the α-secretase pathway and hindering of the β- and γ-secretase pathways (Jayasena et al. 2013).

Overall, these molecules contain two aromatic or inositol groups separated through a backbone of the suitable length (Porat et al. 2006). It can be inferred that the two terminal groups interact with Aβ peptide residues to determine the binding affinity, whereas the linker promotes binding of compounds to specific subregions. It was seen that the polyphenols activity was reduced following the lack of the phenolic functional groups on the aromatic rings (Porat et al. 2006).

It was also established that the linker segment seems to be one of the significant features in amyloid inhibition and the ideal linker region is limited to a fixed length in particular for curcumin, 8–16 Å. The polar functional groups (and often, hydroxyls) commonly exist in inhibitor molecules (Reinke and Gestwicki 2007). Studies have demonstrated that curcumin as a natural polyphenolic antioxidant can decrease Aβ peptide formation from APP and inhibit the Aβ fibrillation into pleated sheets. Yamada and coworkers evaluated the inhibitory activity of curcumin on Aβ peptide (Ono et al. 2004). These in vitro findings showed that curcumin could inhibit $A\beta_{40/42}$ aggregation and destabilize preformed fibrils. Cole et al. showed in vivo (Yang et al. 2005) that curcumin hinders the formation of oligomers and aggregates through its ability to bind to plaques and decrease fibril-derived Aβ toxicity. In order to determine curcumin permeability through the BBB, its ability to bind to Aβ plaques and persuade rapid decomposition of Aβ plaques in brain tissue and the cerebral vasculature, in vivo multiphoton microscopy studies, was applied in mutated mice model of APPs/PS1dE9 which were treated with curcumin for 7 days. The study revealed reduction of existing plaques. In other studies, it was found that curcumin could diminish inflammatory cytokine levels such as interleukin-1b and isoprostanes in the central nervous system (CNS) as well as reduce amyloid plaque burden in transgenic mice (Ringman et al. 2012).

Modeling studies such as molecular dynamics (MD) simulation showed that curcumin plays an important role in the inhibition of Aβ aggregation (Martin et al. 2018). Curcumin has a dual-inhibitor effect on aggregation process; it can serve as a valuable β-sheet breaker agent and as a chelator able to bind to free ions of Cu^{2+} and Fe^{2+}. Epigallocatechin gallate (EGCG) is a natural polyphenolic compound which effectively inhibits conformational transition from a random coil to a β-sheet structure and the formation of Aβ and α-synuclein fibrils (Rezai-Zadeh et al. 2005). This agent can pass through the BBB and may be effective as a prophylaxis agent for AD. In vivo findings showed that it improved spatial cognition learning ability in rats and converted Aβ fibrils and toxic oligomers into smaller nontoxic aggregations (Bieschke et al. 2010).

Natural phytoalexin compounds like resveratrol have beneficial properties such as antioxidative, anti-inflammatory, antimutagenic, and anticarcinogenic (Marambaud et al. 2005). Experimental results indicated that resveratrol exhibited inhibitory activity and neuroprotective effects on Aβ fibrillation and neuronal cells, respectively, and produced nontoxic aggregate species instead of toxic oligomers. This compound reduced secreted and intracellular Aβ peptide by BACE-1 inhibition and also decreased Aβ-associated inflammatory mediators like NF-kappa B by overexpressing and activating the SIRT-1pathway. This agent can degrade intracellular Aβ and reduce extracellular Aβ accumulation through action on the proteasome and stimulating AMPK activity. It was recognized that compounds like resveratrol directly join the natively unfolded polypeptides via effective interactions with the existing aromatic groups, break the π–π contacts, and consequently inhibit their conversion into toxic intermediates.

As noted, EGCG and resveratrol (and their analogs) have undergone phase II clinical trials (Belluti et al. 2013). Recently, 3-morpholinosydnonimine hydrochloride (SIN-1), a synthetic FDA-approved drug in inhibition of platelet aggregation in cardiovascular disease (CVD), has undergone testing for its ability to inhibit amyloid formation (Ren et al. 2017). The in vitro and computational results showed that this drug can effectively inhibit Aβ misfolding and aggregation at different steps of aggregation, prolonging the lag phase, slowing the aggregation rate, and reducing the total amount of fibril formation as well as decreasing Aβ-induced cell toxicity in a dose-dependent manner. It exhibited a remarkable tendency for binding hydrophobic residues I31−M35 and interrupting the formation of the C-terminal β-sheet of Aβ peptide and Aβ−Aβ association (Ren et al. 2017).

Matrine (Mat) is a new natural compound, which is obtained from traditional Chinese herbs to treat dementia. Cui et al. (2017) introduced this compound for inhibition of the Aβ aggregation and blocking the RAGE/Aβ pathway. They discovered that it could inhibit $A\beta_{42}$-induced cytotoxicity and stop the Aβ/RAGE signaling pathway in an AD mouse model. Also, it was observed that it reduced the levels of proinflammatory cytokines and Aβ deposition as well as modulated the memory impairment in AD transgenic mice. Norepinephrine (NE) is a natural neurotransmitter in the body. In vitro and computational results suggest that this compound (Zou et al. 2019) inhibited formation of Aβ aggregation and destabilized Aβ protofibril via formation of H-bonds with residues D1, A2, D23, and A42 in Aβ peptide. In addition, it can reduce inter-peptide β-sheet content and suppress formation of the β-hairpin structure, which leads to a more disordered coil-rich Aβ dimer.

HP-β-Cyclodextrin (HP-β-CD) is a synthetic sugar derivative that is used in drug delivery, genetic vector, environmental protection, and Niemann–Pick disease type C1 (NPC1) treatment. Its efficiency has been investigated as a sugar-

Table 3 Organic molecules–based strategies for inhibition of Aβ peptide aggregation

Number	Structure	Source	Status	Therapeutic effect/category	Ref.
1	Apomorphine	Natural/polyphenolic	In vivo	o Inhibition β-amyloid and α-synuclein formation	(Anguiano et al. 2002)
2	Indolyl-trifluoromethyl-hydroxypropionic acid	Organofluorines	In vitro	o Significant inhibition of the aggregation of Aβ-peptide and disaggregated the existing amyloids	(Török et al. 2006)
3	1,2-Naphthoquinone	Natural/Quinones	In vitro	o Effectively inhibit $A\beta_{42}$ oligomerization	(Necula et al. 2007)
4	1,4-Naphthoquinon-2-yl-L-tryptophan(NQTrp)	Natural/Quinones	In vivo	o Reduction of the $A\beta_{42}$ aggregation o And toxicity with a high molar ratio of NQTrp	(Scherzer-Attali et al. 2010)
5	Oleuropein	Natural/polyphenolic	In vivo	o Inhibition of the formation of soluble toxic oligomers and amyloid fibrils o Reduction of Aβ levels and plaque deposits o Strong improve cognitive performance o Induce autophagy by the regulation of the mTOR pathway	(Rigacci et al. 2011)
6	Myricetin and quercetin	Natural/flavonoids	In vivo/MD	o Neuroprotective and antioxidative effects o AMPK activation o Inhibition of BACE-1 activity o Inhibition of Aβ fibril formation and Aβ-induced toxicity o Inhibition of conformational transition of Aβ Interaction with the surface of the β-sheet via H-bonding and weakening the inter-strand hydrogen bonds	(Ansari et al. 2009; Wang et al. 2015)
7	(2,5-Dichloro-N-(4-piperidinophenyl)-3-thiophenesulfonamide)	Synthetic/sulfonamide	In vitro/in vivo/MD	o Stabilization of native α-helix conformation of $A\beta_{42}$ by interacting with key residues in the central helix region (13–26) with hydrogen bonds and π–π interactions	(Shuaib and Goyal 2018)
8	Trimeric aminopyrazole carboxylic acid	Synthetic	In vitro/MD	o Protection of cells from Aβ lesions o The triethylene glycol spacer as a destabilizing agent of the turn of the U-shaped protofilament	(Hochdörffer et al. 2011)
9	Luminescent oligothiophene penta-formylthiophene acetic acid (LCO p-FTAA)	Synthetic/thiophene	In vitro	o Converting of toxic $A\beta_{42}$ species into nontoxic amyloid fibrils o Visualization of protein aggregation o Formation of less hydrophobic fibrils and more resistant to proteolysis by proteinase K o Reduction of cytotoxicity	(Civitelli et al. 2016)
10	Luteolin and transilitin	Natural/polyphenolic	In vitro/MD	o Potent inhibitors of Ab fibril formation	(Churches et al. 2014)
11	Lovostatin/simvastatin/pravastatin	Synthetic	Phase IV	o A drug approved by FDA o Inhibition of amyloid for AD	(Han and He 2018)
12	Ibuprofen	Synthetic/NSAID	Phase IV	o Drug approved by FDA o Inhibition of amyloid for AD	(Han and He 2018)
13	Bexarotene	Synthetic	Phase II	o Drug approved by FDA as anticancer o Selective tenacity for inhibition of nucleation phase of $A\beta_{42}$ and prolongation of the toxic species production in neuroblastoma cells	(Habchi et al. 2016)
14	Carvedilol	Synthetic	Phase IV	o Drug approved by FDA	

Table 3 (continued)

Number	Structure	Source	Status	Therapeutic effect/category	Ref.
				o Inhibition of amyloid for AD	(Han and He 2018)
15	Ramipril	Synthetic	Phase IV	o Drug approved by FDA o Inhibition of amyloid for AD	(Han and He 2018)

based Aβ inhibitor (Ren et al. 2016). In vitro results indicated that it prevented $A\beta_{42}$ aggregation and Aβ-induced toxicity in a concentration-dependent method as well showing no intrinsic cellular toxicity. Simulation studies showed that it has a high tendency to interact with hydrophobic residues of Aβ at two β-strands and N-terminal domain. It was also reported that carbenoxolone (Cbx), as a natural glycyrrhetinic acid–based compound and FDA-approved drug for the treatment of peptic and esophageal inflammation, has a neuroprotective effect and can stop the aggregation of $A\beta_{42}$ peptide and destabilize the formed fibrillations (Sharma et al. 2017). This agent forms strong interactions with the available residues in the amyloidogenic regions of $A\beta_{42}$ monomers.

Peptides and antibodies

Due to their crucial ability to regulate biological functions, peptides represent another important pharmaceutical choice instead of small organic compound–based drugs. Nowadays, peptides constitute a large fraction of the global drug market due to their unique properties such as high selectivity, low side effects and toxicity, low accumulation in tissues, good tolerance, synthetic viability and practicality, and diversity of chemical and biological synthesis routes, along with a possibility for rational design compared with other therapeutic compounds (Danho et al. 2009). A large number of therapeutic peptides have been proposed as Aβ aggregation inhibitors for treatment of AD (Table 4). Peptides are well-known as β-sheet breakers. Peptide candidates are typically assessed based on their capacity to inhibit Aβ toxicity and self-assembly, prevent conformational transitions, and increase alternative nontoxic fibrillation pathways.

As previously reported, various regions of the Aβ peptide are responsible for the process of Aβ fibrillation. This knowledge is essential for the rational design and development of peptide inhibitors. According to these vital regions the Aβ peptide sequence, the peptide-based inhibitors are divided into two main categories: (1) Aβ sequence-derived peptides and (2) non-Aβ-derived peptide sequences.

Aβ sequence-derived peptides Peptide inhibitors are principally derived from the Aβ peptide based on regions of the central hydrophobic core (CHC) sequence and C-terminal fragments (CTFs). These peptides are homologous to Aβ peptide and hydrophobic feature but have a low tendency to form β-sheets as well as a good binding affinity to Aβ peptide. The central hydrophobic core (CHC) region (residues K16LVFFA21) of Aβ is also known as a key self-recognition sequence or the nucleation site within the Aβ peptide which is responsible for aggregation (Petkova et al. 2002). It was suggested that residues of Ile41 and Ala42 from $A\beta_{42}$ peptide could strongly support stabilization of a new conformation (Li et al., 2011a). Designed short peptides

related to the hydrophobic core residues have been widely investigated as potential inhibitors based on their ability to interact with the full-length Aβ peptide. The CTFs on $Aβ_{42}$ peptide is an important domain with strong rigidity for targeting of Aβ oligomerization. CTFs are able to adjust intermolecular interactions for controlling of $Aβ_{42}$ oligomer formation. The CTF domain reacts with several sites on $Aβ_{42}$ such as C-terminus and N-terminus (Urbanc et al. 2004). Although the natural amino acid–containing peptides are effective inhibitor agents against Aβ aggregation, they suffer from rapid proteolytic degradation in plasma and tend to self-assemble into fibrils during administration and delivery. To overcome these problems and improve their binding affinity to the Aβ peptide, modified peptides with different approaches were utilized (Bruno et al. 2013). These approaches include fluorination, use of D-amino acids, and also the use of retro-inverso cyclization and N-methylation of the ester bond (Goyal et al. 2017; Yan et al. 2013).

Fluorination of the hydrophobic amino acids valine or phenylalanine in the KLVFF sequence can increase the peptide inhibitor activity. Fluorinated amino acids bind to hydrophobic residues of Aβ peptide and interfere with the hydrophobic contacts between Aβ peptide monomers and inhibit their aggregation (Loureiro et al. 2014). D-Amino acid–containing peptides have higher stability against proteolytic enzymes and demonstrate greater affinity when binding to Aβ peptide than their L-isomers. Using animal models, D-peptides were shown to have inhibitor activity against Aβ aggregation (Jagota and Rajadas 2013). Retro-inverso peptides, produced using D-amino acids and flipping the NH and CO groups in the peptide bonds, maintain the same spatial position of the side chain residues and protect the favorable 3D structure in comparison with unmodified L-peptides (Chorev and Goodman 1995). These peptides show advantages with respect to inhibition, higher enzymatic stability, reduced self-assembly, and an improved BBB permeability in an animal model in comparison to L-peptides. Cyclic peptides show strong and specific inhibitor effects towards the formation of amyloid aggregation compared with their noncyclic ones (Luo and Abrahams 2014). Due to their high protease resistance, they are degraded slowly. Methyl group addition to amide groups is a powerful approach in the development of new inhibitors. N-methyl groups can both improve the solubility in aqueous solution and reduce the Aβ toxicity.

Reported N-methylated proprietary peptides such as D-NH_2 (SEN304) (Larbanoix et al. 2011) and SEN1576 can inhibit Aβ-associated toxicity in in vivo studies (Kokkoni et al. 2006; Amijee et al. 2012). Importantly, the SEN304 peptide has been not derived from Aβ sequence and yet is a more potent inhibitor than customized versions of the KLVFF peptide. These peptides can promote Aβ nucleation into nontoxic forms, thereby eliminating toxic oligomers. There are important other factors which can be used in the rational design of peptide inhibitor. Solvent tension is a crucial factor in Aβ aggregation (Ghanta et al. 1996).

Glutamic acid and lysine residues have been recognized as potential enhancing and stabilizing agents (kosmotropes) of Aβ fibrillation through improving the surface tension, while arginine residues have been recognized as inhibitions of aggregation through their action as destabilizing agents (chaotropes) without associating the solvent feature. Tjernberg et al. (1996) demonstrated that Aβ16–20 (KLVFF) plays an important role in disrupting the aggregation of Aβ by binding to full-length Aβ peptides and preventing fibril formation in vitro (Tjernberg et al. 1996). Subsequently, peptides derived from this short sequence were reported for their ability to inhibit the aggregation process. Also, this fragment has been modified using different delivery platforms, such as a dendrimer, polymer, or a few residues of hydrophilic amino acids, in order to improve their physicochemical properties and inhibitory effect on the β-sheet formation.

As previously described, the proline amino acid is a proper β-sheet breaker (Wood et al. 1995). Soto and coworkers rationally entered proline and aspartic acid residues in place of valine and alanine, respectively, to obtain a proline-containing peptide (the LPFFD 5-mer iAβ5) (Soto et al. 1998). This derived peptide from the KLVFF sequence is a β-sheet breaker which can inhibit Aβ aggregation and reduce plaque burden, and neurotoxicity (Soto et al. 1998). Proline prevents the formation of hydrogen bonds in fibrils due to lack of a proton on the secondary substituted nitrogen in the peptide bond. These reported short peptides suffer from rapid degradation by proteolytic enzymes and poor BBB permeability in vivo study (although they showed a significant in vitro efficacy). In order to improve their stability in mice brain and a greater half-life after intravenous (IV) administration, iAβ5p derivate was introduced which had been modified by N-methylation between Pro and Phe residues (Cruz et al. 2004).

The in vitro/in vivo results showed that it has a similar inhibitory effect to the iAb5 peptide against amyloid fibril formation and neurotoxicity but its resistance to protease degradation is greater than shown by the iAb5 peptide. In addition, MD simulations indicate that this peptide has stronger binding and enhanced activity against $Aβ_{40}$ aggregation when compared with the iAβ5 peptide. The KLVFWAK motif was derived from the KLVFF sequence, and a mutation was introduced at the glutamic acid (E22) residue (to lysine (K)) to improve solubility and disrupt self-assembly by electrostatic repulsion (Aoraha et al. 2015). This designed motif targets only C-terminal domain in Aβ oligomers. Results indicated that this motif showed the smallest self-aggregation potential and highest binding affinity to Aβ aggregates and fibrils compared with other peptide candidate. On the other hand, it should have more specificity for reliable detection of Aβ oligomer and fibrils in vivo and ex vivo studies. Towards this aim, D-GRKKRRQRRR-GGGG-DVEFRH (Aβ1−6A2V-TAT)

Table 4 Peptide-based strategies for inhibition of Aβ peptide aggregation

Number	Structure	Status	Therapeutic effect/category	Ref.
1	NAPVSIPQ (NAP)	Failed in phase III clinical trial	o Not derived from Aβ sequence o Modification: polarized amino acids of Q and N, two proline residues, and the hydrophobic backbone o An excellent example of the following investigation	(Ashur-Fabian et al. 2003; Matsuoka et al. 2008)
2	RYYAAFFARR (RR) decapeptide	In vitro	o Design: based on hydrophobic core and the interaction with other sites like turn region or "salt bridge" region target: an extended region $A\beta_{11-23}$ of $A\beta_{40}$ o Stronger binding affinity for $A\beta_{40}$ than LPFFD o Effective inhibition of aggregation and fibrillation o Reduction of induced cytotoxicity by $A\beta_{40}$ self-assembly	(Liu et al. 2014)
3	D-(PGKLVYA) and D(KKLVFFARRRRA)	In vivo	o Derived from the KLVFF sequence o Inhibition of Aβ aggregation and long lifetime in a transgenic model expressing $A\beta_{42}$	(Jagota and Rajadas 2013)
4	ZAb3 affibody	In vivo	o As a dimeric molecule o Binding affinity to the Aβ peptides (nanomolar) o Preventing Aβ aggregation, dissociating preformed oligomers, and facilitating Aβ degradation o Complete inhibition of Aβ aggregation at stoichiometric levels o Selected by phage display technique	(Luheshi et al. 2010)
5	Cyclic peptide CP-2	-	o Nontoxic cyclic peptide o Stabilizing of small Ab oligomers in CP-2 assembled form o Dissolving of formed Aβ fibrils	(Richman et al. 2013)
6	Head-to-tail tandem peptide D3D3 (D-RPRTRLHTHRNRRPRvTRLHTHR-NR)	In vivo	o Not derived from Aβ sequence o An almost twice inhibitory effect on $A\beta_{42}$ oligomer rather than D3 peptide o Conversion of toxic oligomers to nontoxic and amorphous aggregations	(Brener et al. 2015)
7	A sequence-scrambled derivative of D3, RD2 (DPTLHTHNRRRR-NH_2)	In vivo	o Not derived from Aβ sequence o High binding affinity to Aβ and strong reduction of Aβ fibrillation formation o High stability in mouse plasma and organ homogenates o High oral and subcutaneous bioavailability	(Klein et al. 2016; Leithold et al. 2016)
8	FDYKAEFMPWDT (AOEP2)	In vitro	o Not derived from Aβ sequence o A mimotope of the Aβ oligomer o Selected by phage display technique o Binding to all forms of Aβ (monomer, oligomer, and fibrillation) o The significant decrease of pro-inflammatory cytokines TNF-α production	(Zhang et al. 2017)
9	RDLPFFPVRID (iAβ11)	In vitro	o Derived from the KLVFF sequence o A similar degree of hydrophobicity to Aβ (17–21) o Very low propensity to adopt a β-sheet conformation	(Soto et al. 1996)
10	Pentapeptide LPYFD-amide	In vivo	o Derived from the KLVFF sequence o Modification: substation of one Phe by Tyr and the C-terminal COO^- anion with $CONH_2$ o Neuroprotective, tau aggregation properties	(Datki et al. 2004; Granic et al. 2010)
11	Ac-LPFFN-NH_2	In vitro/MD	o Derived from the KLVFF sequence o Effective inhibitor of $A\beta_{40}$ aggregation by stabilization of the native and nonaggregative α-helical conformation of $A\beta_{40}$ o Prolongation of fibril formation by increasing the lag phase	(Minicozzi et al. 2014)
12	D-4F peptide	In vivo	o Not derived from Aβ sequence o Improvement of cognitive function o Inhibition of Aβ peptide deposition	(Handattu et al. 2009)
13	Diazirine-equipped cyclo-KLVF(b-Ph)F	In vitro	o Derived from the KLVFF sequence o Modification: cyclization, diazirine group o Selective binding affinity to $A\beta_{42}$	(Kino et al. 2015)

Table 4 (continued)

Number	Structure	Status	Therapeutic effect/category	Ref.
14	A flavin catalyst attached to an Aβ-binding peptide	In vitro	o Formation of a β-sheet breaker structure by UV-light irradiation o Inhibition of amyloid aggregation, and toxicity of $A\beta_{42}$ o Derived from the KLVFF sequence o Modification: cyclization, attachment of a flavin catalyst inhibition of Aβ aggregation via oxygenation using an artificial catalyst o Decreasing of the aggregation potency and neurotoxicity of Aβ	(Sohma 2016)
15	SGB1 and SGD1 (all D-amino acid pseudopeptides)	MD	o Target: bind to the central hydrophobic region of Aβ, $A\beta_{13–23}$ (R) o The highest ΔG binding to $A\beta_{13–23}$ for SGB1 o More tightly bound SGB1-Aβ42 in the R region than the SGD1 complex o SGB1 may be a better candidate for developing	(Mehrazma et al. 2018)

peptide was designed and evaluated in vivo (Di Fede et al. 2009; Cimini et al. 2016).

The N-terminal fragment of DAEFRH (Aβ1−6) was modified by mutation of alanine 2 to valine and conjugation with the HIV protein transduction domain GRKKRRQRRR (TAT). The TAT motif improves permeability of peptides into/across cell membranes and assists in crossing the BBB. This designed peptide showed great proteolytic stability and higher binding affinity towards $A\beta_{40}$ fibrils than $A\beta_{1–6}$ and inhibited fibrillation formation and elongation in the brain. In order to maximize electrostatic interactions for disrupting in aggregation process and reduce the tendency for self-assembly of the KLVFF segment, RIVFF sequence was designed and modified based on KLVFF sequence using residue mutations of lysine16 (K) to arginine (R) and leucine17 (L) to isoleucine (I) (Ramaswamy et al. 2014).

The results demonstrated that this peptide exhibits reduced surface tension upon self-aggregating into β-sheet structures and may practically enhance cytotoxicity. The two peptides RGKLVFFGR (OR1) and RGKLVFFGR-NH (OR2) are known as retro-inverso peptides (Austen et al. 2008). These peptides derived from the KLVFF sequence were modified via addition of an arginine (R) and glycine (G) residues to enhance their solubility, to prevent self-aggregation, and to act as spacers, respectively. These peptides showed high solubility and stability against proteases while only OR2 peptide demonstrated effective inhibitory effects on Aβ oligomer formation and cytotoxicity. In order to further improve these characteristics, OR2 peptide was modified as HN-rGklvffGr-Ac (RI-OR2) using acetylation of the C-terminal residue (Taylor et al. 2010). The resulting peptide showed high resistance against proteolysis with the same previous inhibitory activity demonstrated in vivo. In another study, the RI-OR2 peptide was conjugated to the TAT peptide to enhance cell membranes and BBB permeability (Parthsarathy et al. 2013). The findings showed that it decreased Aβ aggregation, Aβ plaque levels, and oxidative damages while it enhanced the number of young neurons in the brain.

Ac-LVFFARK-NH2 (LK7) is a peptide derived from the KLVFF sequence via incorporation of two positively charged residues arginine and lysine (R and K) (Xiong et al. 2015). It has been shown to have a dose-dependent inhibitory effect on $A\beta_{42}$ fibrillation process, but due to a high self-assembly properties, it can actually increase cytotoxicity. To reduce this self-aggregation feature and improve inhibitory activity, the LK7 peptide was added to polymers, nanoparticles, and chelators. The LK7 peptide was conjugated onto poly(lactic-co-glycolic acid) NPs. The obtained LK7-PLGA-NPs complex eliminated LK7 self-assembly while also inhibiting $A\beta_{42}$ fibrillation (Xiong et al. 2015). Binding β-cyclodextrin to LK7 (Zhang et al., 2018a) enhanced solubility of LK7 peptide, suppressed its self-aggregation tendency, and improved its binding and inhibitory abilities against Aβ aggregation. Head-to-tail cyclization of LK7 peptide also led to a decrease of the self-assembly propensity of the LK7, an increase of proteolytic stability and binding affinity to the $A\beta_{40}$ peptide. This derivative also can stabilize the $A\beta_{40}$ secondary structure and prevent $A\beta_{40}$-related cytotoxicity. Another derivative of LK7 peptide is Ac-LVFFARKHH-NH2 (LK7-HH) in which LK7 has been attached to the HH ligand as a chelator for capturing free and complexed ions of Cu^{2+} and reducing reactive oxygen species (ROS) production (Zhang et al., 2018a, b, c). This chelator also improved anti-aggregative effects of LK7 against Aβ peptide and reduced its self-aggregation propensity.

Sequences derived from the C-terminal fragments of $A\beta_{42}$, including IIGLMGGVVIA ($A\beta_{31–42}$) and VVIA ($A\beta_{39–42}$), have also been shown to act as inhibitors of Aβ aggregation (Fradinger et al. 2008). It has been shown that the tetrameric $A\beta_{39–42}$ peptide interacts with small oligomers and Aβ42 monomers and locates at several positions, specifically at the N-terminal region in MD simulations. Also, the results

illustrated that VVIA-NH_2 peptide inhibits $A\beta_{42}$ aggregation and $A\beta_{42}$-related toxicity preserving synaptic activity at micromolar levels. However, the acetylated Ac-VVIA sequence did not show these effects (Zheng et al. 2015). The non-acetylated VVIA-NH2 sequence interacts particularly with the C-terminal region while the Ac-VVIA peptide showed a dispersed binding distribution (Zheng et al. 2015). Recently, the Ac-IGLMVG-NH_2 sequence ($A\beta_{32–37}$), a hexapeptide derived from the C-terminal fragment, has been evaluated as an inhibitor of Aβ toxicity in vitro. It revealed a mild efficiency against Aβ-related toxicity (Bansal et al. 2016).

A different class of Aβ aggregation inhibitor was reported that might help the development and improvement of new therapeutics. O-acyl isopeptide (1) and NMe-b-Ala26 (2) ($A\beta_{42}$ derivatives) were introduced as inhibitors (Kawashima et al. 2013). They were derived from the full-length Aβ sequence with modification of an ester bond at the Gly25-Ser26 moiety and an N-methyl amide-β-Ala26, respectively. In vitro results showed that derivative (1) inhibited the formation of $A\beta_{42}$ fibrillation at an equimolar ratio with an inhibitory mechanism different from any other peptidic inhibitors reported so far. Also, this derivative showed more aqueous solubility rather than $A\beta_{42}$ peptides and rapidly decomposed to $A\beta_{42}$ monomers under physiological conditions through an O-to-N acyl rearrangement reaction while derivative (2) exhibited higher chemical stability at physiological conditions.

A novel metalloporphyrin-peptide conjugate based on the KLVFF motif was applied as a fluorescent sensor for detection and visualization of soluble Aβ oligomers in biological fluids (Villari et al. 2017). The zinc-porphyrin compound was covalently attached to the KLVFF motif, and the resulting structure targets histidine residues and hydrophobic region of $A\beta_{42}$. This conjugated compound can enhance amyloid suppression properties and photodynamic therapy as well as inhibition of the cytotoxic effects of $A\beta_{42}$ through the formation of supramolecular bodies with the protein. Gordon et al. (2001) described Apan or PPI1019 (D-(H-((Me-L)-VFFL)-NH_2)) as an N-methylated peptide inhibitor for Aβ aggregation and neurotoxicity. This peptide is currently at phase II clinical trial (Sun et al. 2012).

Non-Aβ sequence-derived peptides The peptide QSHYRHISPAQV (D1) was reported as a peptide inhibitor not derived from the Aβ sequence (Wiesehan et al. 2003). This peptide was selected using a randomized mirror-image phage display technique. Results showed that it interacts with all forms of Aβ peptide (oligomers and fibrils and monomers) and binds specifically to Aβ plaques in the tissue of human brain. It also reduces Aβ aggregation formation and Aβ-associated cytotoxicity at high concentrations. A related peptide D-RPRTRLHTHRNR (D3) was also proposed for inhibition of Aβ aggregation and Aβ-related toxicity (Van Groen et al. 2008). This peptide was not taken from the Aβ sequence and was identified by the mirror-image phage display method. It exhibited great enzymatic stability, good BBB permeability, and efficient bioavailability in oral administration. Moreover, it can bind to Aβ oligomers and convert resulting aggregations to nontoxic amorphous forms via changing of their morphology (Van Groen et al. 2008). In vivo results showed that this peptide decreased Aβ plaque levels and Aβ-related inflammations and improved cognitive impairment in an AD mouse model. Presently, D3 and its derivatives are being tested in phase III clinical trials and are currently at the stage of safety analysis.

Carnosine is a natural imidazole dipeptide molecule which is in muscle and brain tissues. This natural compound was not taken from Aβ sequence, and like a chelator, it can coordinate divalent metal ions (Aloisi et al. 2013). The in vitro and in vivo results showed that it has inhibitory activity against fibrillation process of amyloidogenic species such as Aβ peptide, natural and glycated α-crystallin, and prion protein and reduces their associated toxicity on rat brain endothelial and PC12 cells. This peptide blocks the formation of the intermolecular salt bridge, which is important in stability, and elongation of fibrillation (Aloisi et al. 2013).

Polyclonal antibodies, due to their intrinsic heterogeneity, show inferior biological function to monoclonal antibodies (Dodel et al. 2004). Research has revealed that a monoclonal antibody directed against a single epitope can identify Aβ peptide and suppress its aggregation and cytotoxicity (Du et al. 2003). Previous results have shown that the bapineuzumab monoclonal antibody acts effectively as an Aβ aggregation inhibitor. Other mABs have entered in phase III clinical trial (Nie et al. 2011). These include the solanezumab (LY2062430) monoclonal antibody which was designed as a humanized anti-Aβ peptide immunoglobulin (IgG1). Solanezumab was shown to reduce cognitive and functional decline in AD by lowering Aβ production. Currently, it has completed the phase III clinical trial (Han and He 2018).

Associated challenges with inhibitors of Aβ aggregation

Inhibitor compounds of Aβ aggregation such as metal chelators, nanostructure-based strategies, organic molecules, peptides, and antibodies that interact and bind to specific domains of Aβ highlight new developments of amyloid hypothesis-based therapeutics. These compounds also face challenges and problems that prevent their entrance to clinical uses. For this reason, to date, none of these compounds have proven successful in clinical trials.

It is well that when NPs come into a physiological environment, their surfaces will be immediately covered by

biomolecules such as proteins to produce protein crown-like halos, and the effect of these structures on Aβ fibrillation is currently being evaluated (Salvati et al. 2013). Another important issue with nano-based compounds is their potential toxicity although relatively few studies have reported about long-term toxicity after NP use. It is also known that small molecules produce inadequate steric hindrance effects and are therefore usually unable to inhibit Aβ aggregation (Wells and McClendon 2007). Other important challenges around peptide therapeutic use are BBB permeability, serum stability, and their self-assembly dring storage. In recent years, a tremendous effort has been employed on combatting these limitations.

Conclusion

According to the World Alzheimer Report 2016, nearly 46.8 million people worldwide are currently affected by AD. This number is expected to increase to 131.5 million by 2050 Prince (2015). Yet, there is no cure for AD nor any sensitive clinical tools for the detection and diagnosis of early onset AD. As discussed in this Review, one of the main challenges is that AD is a multifactorial disease that may have different pathologies and etiologies. Specifically, AD can manifest in a molecular sense as Aβ aggregation and fibrillation, tau phosphorylating kinases ROS, and cell cycle proteins. A large body of research suggests that production and aggregation of Aβ peptide causes AD. Therefore, developing methods and tools to inhibit Aβ aggregation will represent a great step forward for AD therapy.

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