Mol Neurobiol (2016) 53:3565–3575
DOI 10.1007/s12035-015-9301-4

Anti-amyloid Aggregation Activity of Natural Compounds: Implications for Alzheimer's Drug Discovery

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Received: 23 February 2015 / Accepted: 9 June 2015 / Published online: 23 June 2015

Abstract Several plant-derived natural compounds are known to exhibit anti-amyloid aggregation activity which makes them attractive as potential therapies to treat Alzheimer's disease. The mechanisms of their anti-amyloid activity are not well known. In this regard, many natural compounds are known to exhibit direct binding to various amyloid species including oligomers and fibrils, which in turn can lead to conformational change in the beta-sheet assembly to form nontoxic aggregates. This review discusses the mechanism of anti-amyloid activity of 16 natural compounds and gives structural details on their direct binding interactions with amyloid aggregates. Our computational investigations show that the physicochemical properties of natural products do fit Lipinski's criteria and that catechol and catechol-type moieties present in natural compounds act as lysine site-specific inhibitors of amyloid aggregation. Based on these observations, we propose a structural template to design novel small molecules containing site-specific ring scaffolds, planar aromatic and nonaromatic linkers with suitably substituted hydrogen bond acceptors and donors. These studies will have significant implications in the design and development of novel amyloid aggregation inhibitors with superior metabolic stability and blood-brain barrier penetration as potential agents to treat Alzheimer's disease.

Keywords Alzheimer's disease · Beta-amyloid · Natural compounds · Molecular docking · Pharmacophore modeling

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Overview of Alzheimer's Disease

Alzheimer's disease (AD) is a progressive neurodegenerative disorder that slowly destroys memory and cognition in the elderly population [1]. The major histopathological hallmarks of AD are extracellular senile plaques, consisting of abnormally aggregated amyloid-beta (Aβ) peptide [2]. To date, available drugs only treat the symptoms of AD and no therapies are able to prevent or fundamentally treat the disease.

Amyloid aggregation is a critical step for Aβ to form neurotoxic species and their deposition in the brain, leading to neuroinflammation, neurite degeneration, and neuronal death causing cognitive decline [3]. The therapeutic strategies for AD mainly focus on inhibiting Aβ production (such as β- and γ-secretase inhibitors), facilitating Aβ clearance (such as Aβ immunotherapy [4]), and blocking Aβ neurotoxicity by inhibiting the formation of various forms of Aβ aggregates. However, most researchers focus on the first two strategies but have encountered various challenges. As the monomeric Aβ is less toxic, keeping Aβ from self-assembling into toxic dimers, oligomers, protofibrils, and fibrils can reduce its toxicity. Aggregation of monomeric Aβ could be reduced in the presence of many natural compounds such as epigallocatechin gallate [5], curcumin [6], resveratrol [7], and scyllo-inositol [8], which offer examples for us to screen and design inhibitors of Aβ aggregation. In this review, we discuss the effects of the natural compounds on Aβ aggregation and

neurotoxicity, analyze the active motif of their structures, and propose perspectives for designing new AD therapeutic compounds to target Aβ aggregation and its toxicity.

Role of Aβ Aggregation in AD Pathogenesis

The 4-kD Aβ monomer is consistently produced by proteolytic cleavage of the amyloid precursor protein (APP) by β-secretase (BACE 1) and γ-secretase. The recent finding that a rare mutation in the APP decreases production of Aβ and protects against AD strongly supports the fact that Aβ plays a crucial role in the pathogenesis of AD [9]. The neurotoxicity of the amyloid peptide depends on its peptide length and conformation. Aβ40 accounts for more than 90 % of total Aβ, while Aβ42 is more prone to aggregate and is the predominantly more toxic peptide [10, 11]. A little increase in the Aβ42:Aβ40 ratio stabilizes toxic Aβ oligomeric species [12]. In vitro and in vivo studies suggest that Aβ causes synaptic dysfunction, abnormal iron homeostasis, oxidative stress, mitochondrial dysfunction, energy hypometabolism, and memory impairment [13–19]. Monomeric Aβ was shown to be nontoxic and prevents neuronal cell death caused by oxidative stress [20]. The toxic effects of aggregation-prone Aβ result from conformational transition of Aβ monomers from predominantly α-helical to β-sheet structures that result in monomeric Aβ aggregation and fibrillization. The assembly forms of Aβ include oligomers, protofibrils, fibrils, and plaques, the neurotoxicity of which is different from one another. Numerous studies indicate that soluble Aβ oligomers play important causal roles in AD (reviewed in [21]), and Aβ42 oligomers are thought to be the most toxic form [22]. Therefore, the aggregation of amyloid peptide is a pivotal step in AD pathogenesis, and inhibiting Aβ aggregation is an attractive neuroprotective strategy for the prevention and treatment of this disease.

Aggregation and Neurotoxic Properties of Aβ and the Related Motifs

The amino acid sequence of Aβ42 is NH_2-DAEFRHDSGYEVHHQKLVFFAEDVGSNKGA IIGL MVGGVVIA-COOH. Residues 1–28 and 29–42 respectively represent a hydrophilic domain and a hydrophobic domain. The natively unfolded monomeric Aβ primarily have a random-coil structure in their soluble state when they are released into extracellular matrix [23]. However, conformational transition of Aβ from native state to β-sheet happens rapidly, which initiates the aggregation process and forms toxic Aβ oligomers [24, 25]. The monomeric Aβ peptide self-assembles through multiple pathways, and aggregated Aβ conformers range from dimers, soluble oligomers to fibrillar oligomers, protofibrils, and fibrils [26–29]. As toxic Aβ oligomers are not an obligate intermediate on the pathway to fibril formation [30], selectively inhibiting oligomerization but not affecting fibrillization is also a possible target to attenuate Aβ toxicity. Although the exact mechanism of Aβ aggregation is not completely clear, the key structure related to Aβ aggregation will be discussed, which may assist in understanding the aggregation process and to design new compounds as Aβ aggregation inhibitors and thus attenuate its toxicity.

The Aβ region consisting of amino acids 12–24 and 30–40, known as the fibril-forming Aβ fragment, is responsible for their native states self-assembling into a β-sheet structure [4], and *N*-methylated residues at this fragment effectively inhibit the formation of intermolecular hydrogen bonds required for peptide oligomerization into β-sheet aggregates [31]. Several small molecules that bind to the C-terminus of Aβ42 and exhibit hydrophobic and hydrogen-bonding interactions have also been designed to inhibit β-sheet formation [32, 33]. Some studies suggest that β-sheet conformation in residues 24–28 promote Aβ oligomerization [34, 35]. Thus, a β-sheet structure is necessary for Aβ oligomerization and neurotoxicity. Therefore, preventing the conformational transition of the Aβ monomer from an initial random coil or α-helix into a β-sheet is the primary goal of blocking Aβ toxicity by small-molecule inhibitors.

The Aβ monomer consists of aromatic residues, phenylalanine (Phe^4, Phe^{19}, and Phe^{20}) and tryptophan (Tyr^{10}) [36]. Pi-stacking interactions between aromatic residues were suggested to play a significant role in the Aβ self-assembly process by enhanced fibril assembly kinetics [37, 38]. The rodent Aβ peptide sequence is identical to the human Aβ sequence except three amino acids located within the N-terminal domain of the Aβ peptide (Arg-to-Gly, Tyr-to-Phe, and His-to-Arg). However, most of these rodent species lack AD-like pathology [39]. Thus, the three specific sites are believed to be important in Aβ aggregation or Aβ-induced neurotoxicity. Substitution of the amino acid residue Tyr^{10} with alanine or phenylalanine in the Aβ peptide led to a dramatic decrease in neurotoxicity, suggesting that tyrosine is important in Aβ-induced neurotoxicity [40, 41]. Substitution of histidine (His^{13}) in rodent Aβ can disrupt the zinc binding site and subsequently alleviates zinc-induced aggregation in vitro [42]. In addition, oxidation of methionine (Met^{35}) can promote toxic conformations in Aβ oligomers [43]. Although their role in Aβ aggregation still needs to be further clarified, these findings help us better understand the structural perturbation of Aβ to its aggregation.

It has been shown that biometals (e.g., iron, zinc, and copper) are significantly enriched in the brains of AD patients compared with normal age-matched subjects [44, 45], which may promote Aβ oligomerization [46] and stabilize soluble Aβ oligomers [47]. The residues Tyr^{10}, His^{13}, and His^{14} of Aβ are investigated as potential metal ion coordination

centers [48, 49]. So compounds that could act as biometal chelators may also reduce Aβ oligomerization.

Natural Compounds Targeting Aβ Aggregation and Toxicity

A wide range of natural and synthetic molecules (both large and small molecules) has been investigated for their ability to counteract Aβ aggregation and toxicity [50]. In this review, we will focus on some natural compounds that are known to exhibit anti-Aβ activity and will address the mechanisms of their inhibition. The discussion on synthetic molecules with anti-Aβ activity is beyond the scope of this review. Polyphenol-containing natural compounds are known to exhibit multi-target effects on AD including antioxidant, free radical-scavenging properties, anti-amyloidogenic activity, cell signaling modulation, telomere length, and modulation of the sirtuin proteins [51]. Many compounds were shown to inhibit the formation of Aβ fibrils or to destabilize preformed Aβ fibrils by binding directly to monomeric Aβ or mature aggregates [52]. But disassembly of large fibrils raises concerns of increasing load of Aβ oligomers and causing secondary damage to neurons, which is defined as the "raising dust" effect [4]. Thus, compounds that convert mature Aβ fibrils into smaller or nontoxic aggregates and avoid regeneration of toxic aggregation intermediates are attractive candidates to attenuate Aβ toxicity. In the following section, some natural compounds with amyloid aggregation inhibition properties are discussed.

Epigallocatechin Gallate

Epigallocatechin-3-gallate (EGCG, Fig. 1), the principal polyphenol present in green tea, has been shown to promote the formation of unstructured, nontoxic Aβ aggregates by inhibiting its conformational change from a random-coil to a β-sheet structure [5, 53]. The small Aβ oligomers formed in the presence of EGCG were nontoxic and unable to seed further fibril growth [54]. Solid-state nuclear magnetic resonance (NMR) analysis revealed that the N-terminus residues 1–20 become unstructured, whereas residues 22–39 adopt a β-sheet conformation. Furthermore, EGCG is able to remodel mature Aβ fibrils and toxic oligomers into smaller nontoxic aggregates with loss of β-sheet content [55]. This remodeling effect may be via alternative hydrogen bonding facilitated by the hydroxyl-rich EGCG [5]. There are 12 important residues of Aβ that strongly interact with EGCG (Phe^{4}, Arg^{5}, Phe^{19}, Phe^{20}, Glu^{22}, Lys^{28}, Gly^{29}, Leu^{34} to Gly^{37}, and Ile^{41}), while the side chains of some hydrophobic residues (Phe, Met, and Ile) and the main chains of Lys^{28} and Gly^{29} provide nonpolar interactions that contributes more than 71 % to the binding free energy of the EGCG-Aβ complex [56]. Another study

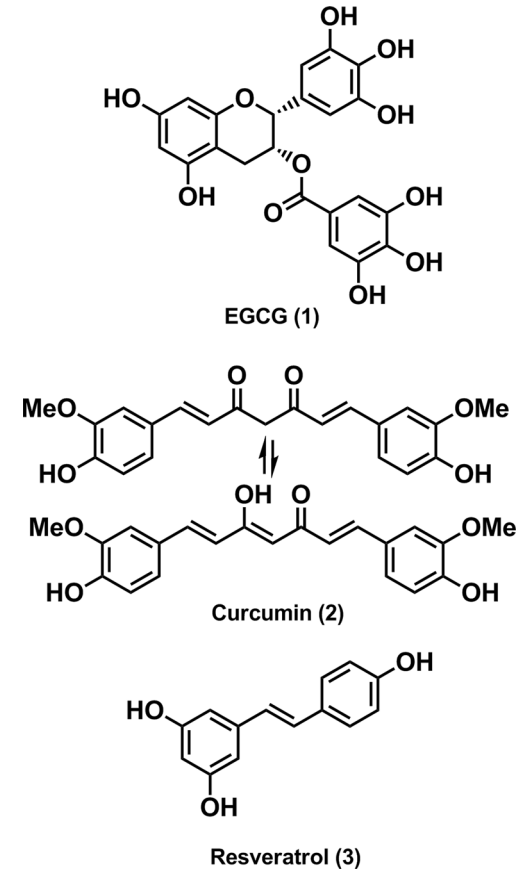

Fig. 1 Chemical structures of epigallocatechin gallate (EGCG), curcumin tautomers, and resveratrol

shows that when free amines or thiols of Aβ are proximal to the EGCG hydrophobic binding sites, the EGCG-based quinones are capable of covalently modifying Aβ through the formation of Schiff base [57]. Therefore, the combination of hydrophobic interaction and Schiff base formation between oxidized EGCG and Aβ may be responsible for its remodeling effect. EGCG displays the anti-aggregation effect from mainly two pathways: first, EGCG binds to the native form of Aβ through interactions with the side chains of specific residues, and second, EGCG binds to the misfolded Aβ species with noncovalent interactions involving Aβ backbone and subsequently remodels toxic aggregates into small nontoxic, off-pathway oligomers.

Curcumin

Curcumin ((1*E*,6*E*)-1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione, Fig. 1), a diphenol isolated from the rhizomes of *Curcuma longa* (turmeric), was first shown to decrease the levels of insoluble and soluble Aβ and plaque burden in Tg2576 transgenic mice [58]. It binds to both Aβ oligomers and Aβ fibrils [59]. The anti-aggregating activity of curcumin against Aβ has been actively investigated. Curcumin is believed to inhibit Aβ oligomerization, promote

the deposition of nontoxic Aβ fibrils, and decrease the neurotoxicity of Aβ aggregates [6, 60]; thus, it may be capable of changing or accelerating the pathway from toxic Aβ oligomers to nontoxic Aβ forms. In addition, curcumin was shown to accelerate Aβ fibril conversion by reducing the prefibrillary species of Aβ, and hence alleviate Aβ toxicity in the transgenic *Drosophila* model [61]. Modeling studies have shown that curcumin can act as an efficient β-sheet breaker [62]. Furthermore, curcumin was shown to bind Cu^{2+} and Fe^{2+} ions, which could also play a role in inhibiting Aβ aggregation [63].

Numerous studies have tried to identify structural features that contribute to the anti-oligomerization activity of curcumin and its analogs. An early study indicated that Aβ inhibitors interact with GxxxG motifs (i.e., Gly33 in Aβ40 and Gly37 in Aβ42) in the C-terminus of the Aβ fibrils [64]. The enolic center and the two phenolic polar groups separated by a hydrophobic bridge make it prone to binding to Aβ oligomers [65]. Solid-state NMR analysis reveals that the methoxy and/or hydroxy groups of curcumin interact with the V^{12} and $^{16}KLVFFA^{21}$ residues of the Aβ [66, 67]. They emphasized that the enone group and unsaturated carbon spacer between aryl rings are essential for its anti-Aβ aggregation activity. Recent studies show that the pi-stacking interaction between curcumin and the aromatic residues (Tyr, Phe, and His) of Aβ contributes to the reduction of the β-sheet content in the Aβ dimer [62]. According to the previous findings, the coordination of copper with imidazoles on His13 and His14 of Aβ could initialize Aβ aggregation [68, 69]. This led to the design of imidazole-containing curcumin analogs as new tracers of Aβ oligomers and aggregation inhibitors of Aβ capable of specifically interrupting the coordination of copper and imidazoles from His^{13} and His^{14} [70].

Resveratrol

Resveratrol (3, 5, 4′-trihydroxystilbene, Fig. 1), a nonflavonoid polyphenol abundant in red wine and many plants, consists of two aromatic rings joined by a methylene bridge and is known to possess a wide range of biological effects [71]. Several studies indicate that the neuroprotective effects of resveratrol on AD is attributed to a number of factors, including attenuation of Aβ-induced toxicity [72], reduction in secreted and intracellular Aβ via BACE-1 inhibition [73], and intracellular degradation of Aβ via proteasome [74]. It can also lower extracellular Aβ accumulation by increasing AMPK activity to trigger autophagy and lysosomal degradation of Aβ [75]. It reduced Aβ-stimulated NF-kappa B signaling by overexpressing and activating SIRT-1 [76]. But how resveratrol interacts with the neural cell and enhances its intracellular degradation of Aβ is unclear. Whether there exists a receptor of resveratrol on the neural cell membrane deserves further consideration.

Most notably, resveratrol was able to directly interfere with the Aβ aggregation. Resveratrol was proved to directly interact with Aβ monomers and fibrils, inhibit Aβ fibrillization, and convert toxic oligomers into nontoxic species [77, 78]. Resveratrol derivatives were also shown to inhibit Aβ42 aggregation by targeting the C-terminus and inhibiting the formation of β-sheets [79]. Others found resveratrol selectively remodeled certain Aβ conformers that possess β-sheet structures into nontoxic, unstructured species [7]. The remodeling activity may result from the interaction between resveratrol and aromatic side chains (e.g., Phe^4, Tyr^{10}, Phe^{19}, Phe^{20}) of Aβ. Thus, the interaction between resveratrol and the N-terminal of Aβ is able to disaggregate mature aggregates into nontoxic species, although the N-terminal of Aβ is hidden in mature aggregates. A glycoside of resveratrol was shown to disaggregate Aβ soluble oligomers at sub-stoichiometric concentrations [7]. Researchers found that polyphenol aglycones and glycosides were able to remodel toxic Aβ oligomers into nontoxic, off-pathway conformers [80]. Thus, the phenolic rings are responsible for its remodeling activity and the minimal structural requirement for phenolic aglycones to remodel Aβ oligomers consists of two aromatic rings, of which at least one must possess a hydroxyl substituent.

Flavonoids

Flavonoids, especially myricetin and quercetin (Fig. 2), exhibit neuroprotection in AD by multiple mechanisms, such as antioxidative effect [81, 82], AMPK activation [83], and inhibition of BACE-1 activity [84]. Quercetin possesses a strong ability to inhibit Aβ fibril formation and protects neuronal cells against Aβ-induced toxicity [85]. Myricetin was shown to prevent conformational change of Aβ from a random-coil to a β-sheet-rich structure, and its inhibitory effects against Aβ aggregation were directly proportional to the number of hydroxyl groups on the B ring [86]. Another study reached the same conclusion that the 3′,4′-dihydroxyl group was essential for their inhibition of Aβ aggregation [87]. A multimethodological study also proved that myricetin inhibits Aβ aggregation by targeting preferentially Aβ monomers and short transient oligomers [88]. Computational analysis showed that myricetin interacts with the surface of the β-sheet via H-bonding, weakening the interstrand hydrogen bonds and eventually disrupting the outer layer of the aggregate [89]. In addition, the integrated catechol moiety of flavonoids performs a bifunctional inhibitory activity (metal chelation and Aβ interaction) against Aβ aggregation by interacting with the metal binding site on Aβ via their α-keto enolate group [90, 91]. Furthermore, oxidizing the residue methionine (Met^{35}) in Aβ monomers, which hinders the amyloidogenic conformation, is also the potential mechanism for anti-aggregation of myricetin as revealed by mass spectrometry experiments [92]. Other flavonoids with potential

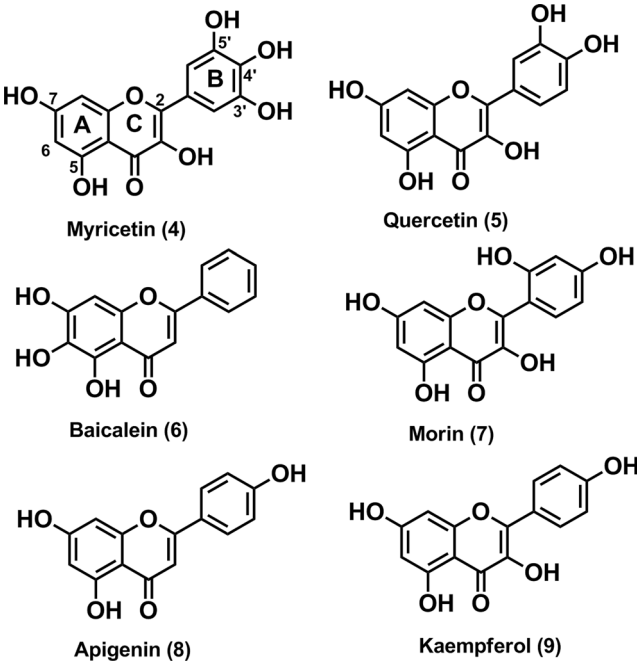

Fig. 2 Chemical structures of flavonoids myricetin, quercetin, baicalein, morin, apigenin, and kaempferol

Aβ aggregation inhibition include baicalein [93], morin [94], apigenin [95], and kaempferol [89] shown in Fig. 2.

Others

Extra virgin olive oil (EVOO) was shown to improve cognitive decline associated with aging and disease [96–98]. Oleuropein, the functional component of EVOO, was investigated to inhibit Aβ aggregation and toxicity in vitro and in vivo. It was shown to interact with the monomeric form of Aβ or its oxidized form Aβ Met^{35}(O) by noncovalent binding [99], and the hydrophobic region of Aβ (^{16}KLVFFA^{21}), a critical Aβ sequence implicated in its aggregation, was most likely to interact with the nonpolar moiety of oleuropein [100, 101]. *Caenorhabditis elegans*, a simplified model of AD, showed significant reduction of Aβ plaque deposition and toxic oligomer formation after the administration of oleuropein aglycone (OLE, Fig. 3) [102]. This compound also strongly improved cognitive performance of a young/middle-aged TgCRND8 mouse model of AD. They found that OLE was able to induce autophagy possibly by the regulation of the mTOR pathway in cell cultures [103].

Isoliquiritigenin (ISL, compound **11** in Fig. 3), a trihydroxychalcone, is one of the components of licorice. It possesses an α,β-unsaturated system similar to curcumin. A series of new ISL derivatives were designed as inhibitors of Aβ aggregation and cytotoxicity by decreasing the β-sheet structure [104]. Yet another natural product, cyaniding 3-*O*-glucopyranoside (Cy-3G, Fig. 3), derived from fruit and

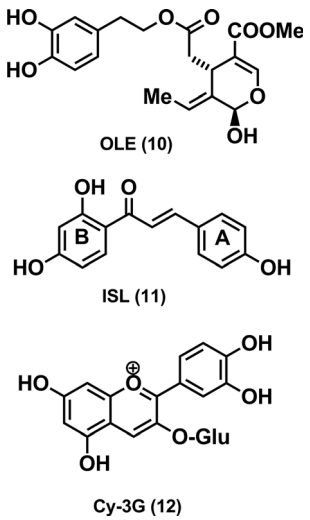

Fig. 3 Chemical structures of oleuropein aglycone (OLE), isoliquiritigenin (ISL), and cyanidin-3-*O*-glucopyranoside

vegetables, prevents the formation of soluble Aβ25–35 oligomers and their neurotoxicity in SH-SY5Y cells [105], which is probably due to the presence of a polyphenol-like structure with many hydroxyl groups, which could interact with amino acid residues in the Aβ25–35 peptide through hydrogen bonds. Other natural compounds that exhibit anti-Aβ aggregation properties include rosmarinic acid (RA), nordihydroguaiaretic acid (NDGA), and ferulic acid (FA) as shown in Fig. 4. The large molecular weight natural compound tannic acid [106] is metabolically unstable and is expected to degrade to smaller fragments (gallic acid, a trihydroxybenzoic acid) whereas the inositol isomer scyllo-inositol is known to bind to amyloid-forming peptide fragment Aβ (^{16}KLVFFA^{21}), coat the surface of Aβ protofibrils, and disrupt their lateral stacking into amyloid fibrils [107].

Overall, the anti-Aβ aggregation mechanisms of all these natural compounds discussed can be due to their ability to

a) Increase the stability of amyloid peptides in the native state
b) Inhibit the formation of toxic oligomers by preventing the required conformational transition and or by acting as a biometal chelator
c) Disassemble toxic Aβ species into nontoxic forms
d) Inhibit toxic Aβ oligomer interaction with the cell membrane by selective neutralization of the toxic Aβ structure epitope

Computational Studies of Natural Compounds with Aβ

In order to understand the anti-amyloid activity of natural compounds shown in Figs. 1, 2, 3, and 4, we first investigated

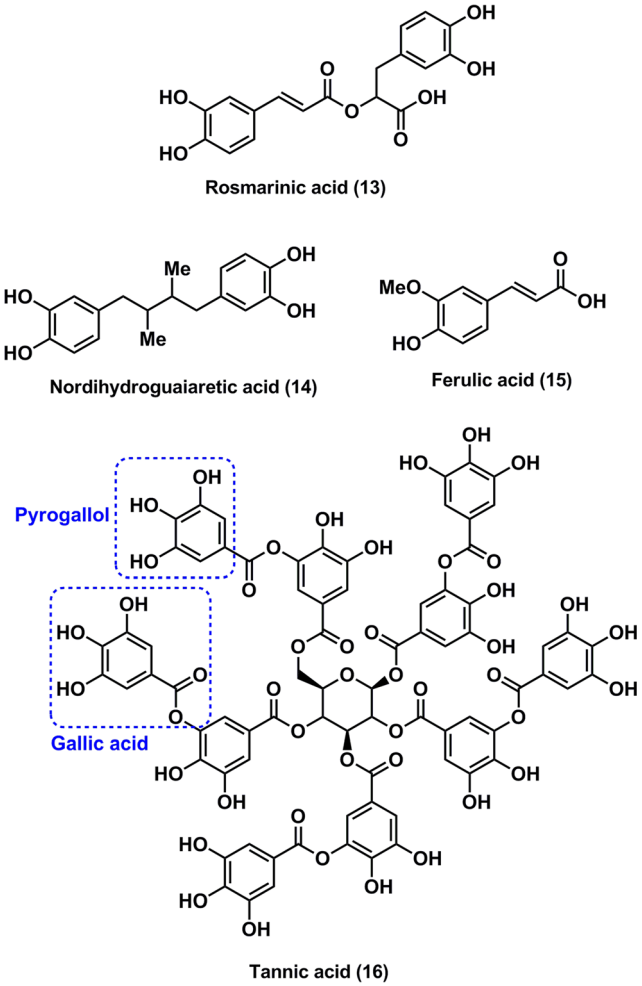

Fig. 4 Chemical structures of rosmarinic acid, nordihydroguaiaretic acid, ferulic acid, and tannic acid

the binding interactions of ligands with Aβ. This was carried out by molecular docking studies using the CDOCKER program (BIOVIA/Accelrys Inc) [108]. The steric zipper assembly of Aβ hexapeptide ^{16}KLVFFA^{21} was used to obtain the most stable ligand-peptide complex [109]. We focused our attention on the flavonoid class of polyphenolic compounds represented by myricetin, quercetin, baicalein, morin, apigenin, and kaempferol (Fig. 2). These molecules contain a common pharmacophore 2-phenylchromen-4-one. The Aβ hexapeptide ^{16}KLVFFA^{21} steric zipper assembly is a useful model to study the binding modes of ligands with anti-amyloid activity [110, 111]. The spine of the steric zipper assembly contains amino acid side chains of lysine, leucine, and phenylalanine. The flavonoids underwent polar and nonpolar interactions with these amino acids. Investigating the binding modes of flavonoids shows that in general the 2-phenylchromen-4-one pharmacophore was oriented in the core of the steric zipper assembly. Furthermore, in the case of both myricetin and quercetin, their *C*-2 3,4,5-trihydroxylphenyl and 3,4-dihydroxyphenyl substituents respectively were oriented in the vicinity of lysine amino acid side chains and underwent polar contact (Fig. 5). The binding mode of baicalein shows that the 5,6,7-trihydroxy-2-phenylchromen-4-one was oriented closer to lysine amino acid side chains at the steric zipper interface. Interestingly, the common feature seen with these flavonoids was the fact that the 3,4-dihydroxy substituents underwent polar contacts with lysine amino acid side chains as shown in Fig. 5. It should be noted that the KLVFFA region of Aβ is known to play a significant role as a seeding point in the nucleation-dependent aggregation [110, 112]. Docking studies suggest that flavonoids that contain catechol groups or adjacent dihydroxy (3,4-dihydroxy) substituents such as myricetin, quercetin, and baicalein are able to exhibit superior anti-Aβ aggregation properties due to their ability to undergo polar contacts with lysine chains compared to flavonoids that lack catechol, catechol-type, or 3,4-dihydroxy substituents such as morin, epigenin, and kaempferol (Fig. 2). These observations are further supported by a recent work from Sato and coworkers which show that catechol-containing flavonoids can undergo oxidation in vivo to form quinone intermediates. These quinone intermediates can potentially link covalently to lysine side chains and prevent Aβ aggregation [113].

Docking studies of other natural compounds containing catechol groups (EGCG **1**, OLE **10**, and Cy-3G **12**, Figs. 1 and 3) exhibit similar binding modes with their catechol groups interacting with lysine side chains in the Aβ-hexapeptide model. The resorcinol containing natural compounds resveratrol **3** (Fig. 1) and ISL **11** (Fig. 3) binding indicates that the resorcinol groups were interacting with lysine side chains whereas the aromatic rings underwent nonpolar contacts with leucine, phenylalanine, and valine side chains. Our work has shown that the enol form of curcumin is primarily responsible for its anti-Aβ activity and the 4-hydroxy-3-methoxy substituents on the phenyl ring undergo polar contacts with lysine side chains whereas the aromatic rings were involved in nonpolar contacts with leucine, phenylalanine, and valine side chains in the Aβ-hexapeptide steric zipper assembly [114].

In order to understand the structural features that are required to exhibit anti-Aβ aggregation activity, we constructed a ligand-based pharmacophore model for flavonoids using the HipHopRefine algorithm in BIOVIA/Accelrys Inc. Structure-Based-Design software (Fig. 6a, b). The pharmacophoric map was generated by using a training set of flavonoids made up of their bioactive conformations (Fig. 6a) bound to the Aβ hexapeptide ^{16}KLVFFA^{21} steric zipper model. The flavonoid myricetin, which is known to be the most potent inhibitor of amyloid aggregation, was used as the reference compound to generate the pharmacophore model by including hydrogen bond donor (HBD), hydrogen bond acceptor (HBA), and aromatic ring (AR) parameters (Fig. 6b). The top-ranking pharmacophore model for flavonoids suggests that structural

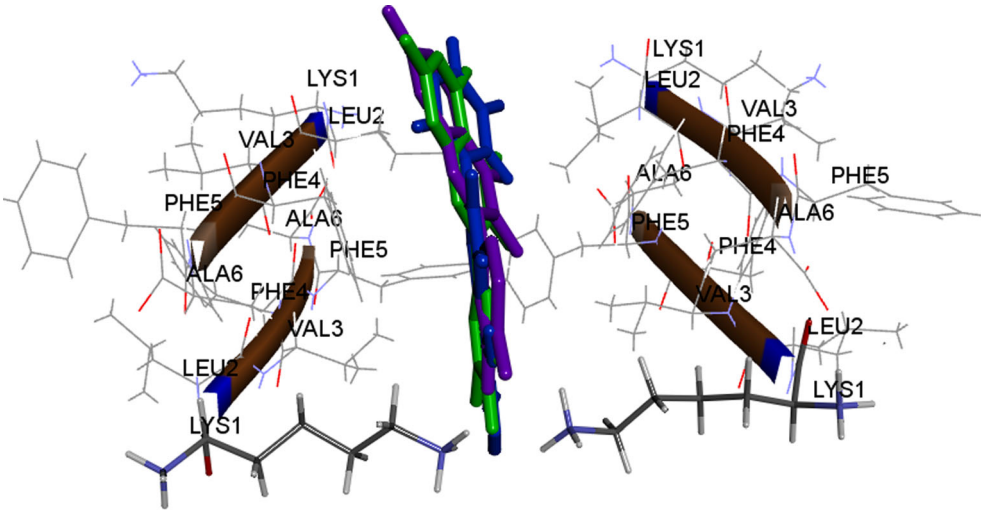

Fig. 5 Binding modes of myricetin (*green*), quercetin (*violet*), and baicalein (*blue*) in the Aβ-hexapeptide KLVFFA tetramer steric zipper model (pdb id: 3OVJ)

requirements for Aβ aggregation inhibition includes the presence of (i) three HBDs; (ii) two HBAs; and (iii) two ARs and that these features should be separated from a distance range of 2.73–7.40 Å (Fig. 6a). It should be noted that these features correlate with the molecular docking results of flavonoids myricetin, quercetin, and baicalein where the presence of adjacent HBDs (catechol and catechol-type groups respectively) leads to favorable interactions with lysine side chains.

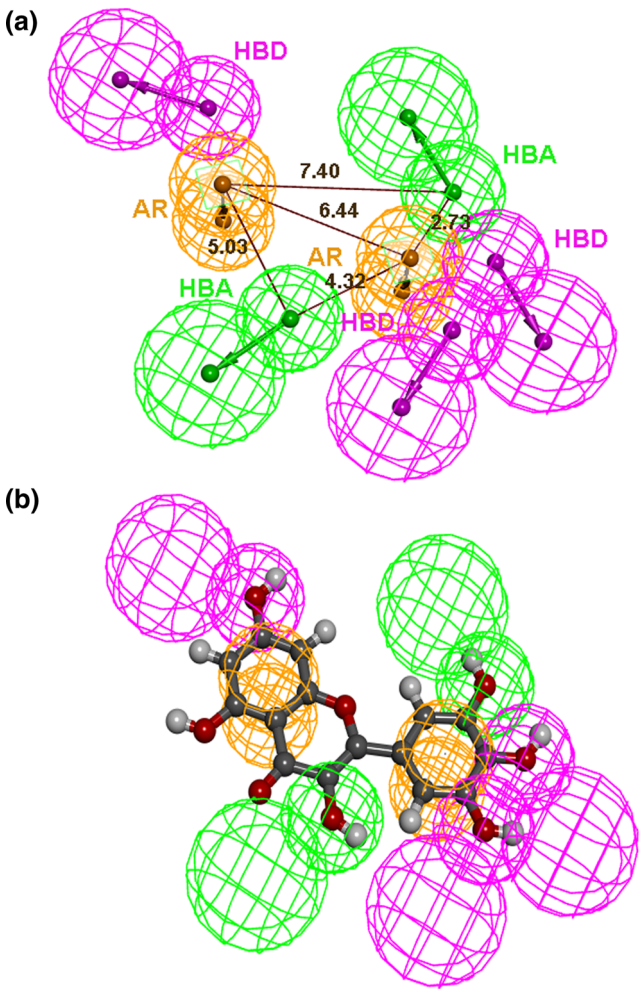

Fig. 6 **a** Pharmacophore model for flavonoids with HBDs, HBAs, ARs, and distance constraints; **b** myricetin mapped into the pharmacophore model. *Color codes*: *pink*=HBDs; *green*=HBAs, *orange*=ARs

Perspectives for the Design of New Compounds with Anti-Aβ Aggregation Properties Based on Natural Compounds

Natural compounds possessing polyphenolic groups are known to exhibit antioxidant and metal-chelating properties that are associated with their beneficial effects. Our studies on natural compounds **1**–**16** (Figs. 1, 2, 3, and 4) and their binding modes using the Aβ-hexapeptide model highlight the importance of certain ring scaffolds as structural requirement to exhibit anti-Aβ aggregation properties in the design of novel molecules. These requirements include substituents such as (i) phenol; (ii) catechol; (iii) resorcinol; (iv) 3,4,5-trihydroxyphenyl (pyrogallol); and (v) hydroxy-methoxyphenyl ring scaffolds linked together by planar core templates such as a 2-phenylchromen-4-one ring (flavonoids) or an α,β-unsaturated system (curcumin **2** and ISL **11**, Figs. 1 and 2) and carbon-carbon double bonds (resveratrol) as shown in Fig. 7. This suggests that small molecules with planar geometry and capable of exhibiting linear extended conformation are able to bind at the β-sheet interface with the ability to convert neurotoxic Aβ aggregates to nontoxic forms. Furthermore, in the design of novel anti-Aβ agents, the presence of catechol or catechol-type substituents is expected to exhibit superior Aβ inhibition due to their potential to covalently link to lysine side chains at the β-sheet interface [110, 113]. Table 1 gives a summary of physicochemical properties of natural compounds **1**–**16**. The

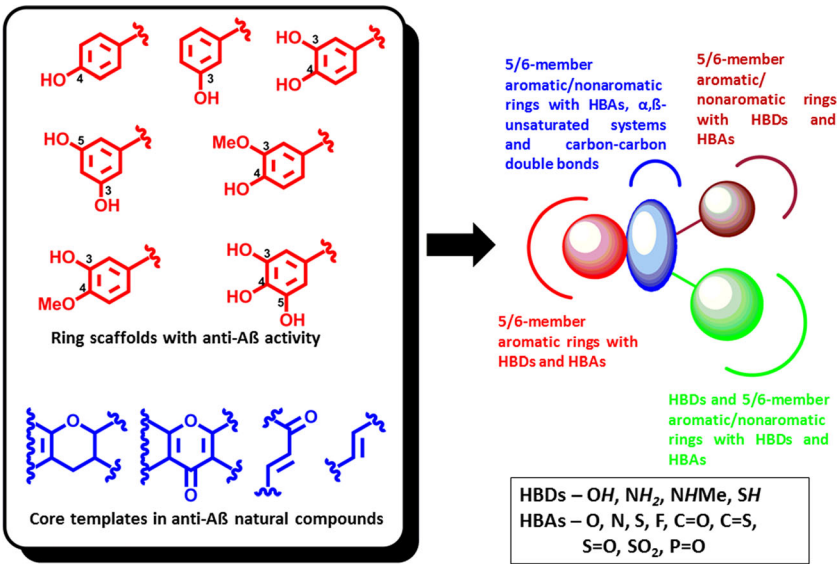

Fig. 7 Schematic on designing novel small molecules with anti-Aβ activity inspired by natural compounds

general trend seen with the exception of compound **16** indicates that the minimum requirement for anti-Aβ activity is the presence of (i) one aromatic ring; (ii) two hydrogen bond donors; (iii) three hydrogen bond acceptors; (iv) one rotatable bond; (v) molecular volume range of 150–329 Å^3; (vi) lipophilicity range with AlogP values 1.18–4.70; and (vii) molecular weight ranging from 194 to 458. These physicochemical parameters fit Lipinski's rule of five [115]. It should be noted that polar polyphenolic natural compounds such as **4**, **5**, **11**, and **12** (Figs. 2 and 3) exhibit weak blood-brain barrier (BBB) penetration and can undergo metabolic changes in the gut, while some lipophilic compounds are capable of entering the brain and reaching levels higher than the physiological

Table 1 Some physicochemical properties of natural compounds **1–16**

Compound	Number of H-bonds[a]		Molecular volume (Å^3)[b]	AlogP[c]	Molecular weight
	Donors	Acceptors			
1	8	11	328.6	3.09	458.37
2	2–3	6	293–294	3.55–3.57	368.38
3	3	3	182.1	3.09	228.24
4	6	8	225	1.38	318.23
5	5	7	209.2	1.63	302.23
6	3	5	198.2	2.41	270.23
7	5	7	209.2	1.63	302.23
8	3	5	198.2	2.41	270.23
9	4	6	207.5	1.87	286.23
10	3	8	301.5	1.91	378.37
11	3	4	196.2	2.97	256.25
12	8	10	326.9	1.18	449.38
13	5	8	271.6	2.7	360.31
14	4	4	252.1	4.7	302.36
15	2	4	150.2	1.66	194.18
16	25	46	1177.5	8.81	1701.19

[a] The number of hydrogen bond donors and acceptors were calculated using the *Discovery Studio* program using CHARMm force field

[b] Molecular volume was calculated using the *Discovery Studio* (BIOVIA/Accelrys Inc) program energy minimization

[c] AlogP was calculated using the *Discovery Studio* program

concentration of soluble Aβ in the brain [60, 116–118]. Thus, the development of new compounds with superior in vivo metabolic stability and BBB penetration is critical.

In this regard, Fig. 7 gives a summary of critical structural features that can be incorporated in the design of novel small-molecule inhibitors of Aβ aggregation. It is anticipated that catechol and catechol-type scaffolds can act as site-specific Aβ aggregation inhibitors with the ability to link covalently to lysine side chains whereas other HBAs including C=O, C=S, and P=O can exhibit reversible binding to lysine side chains and the potential to reduce the toxicity of various Aβ aggregates [119]. These site-specific scaffolds can be fused to planar aromatic or nonaromatic rings or aliphatic linkers substituted with suitable HBDs and HBAs as shown in Fig. 7.

In summary, this review highlights the critical structural features present in natural compounds that are responsible for their ability to prevent Aβ aggregation and provides a structural template to design new small molecules as therapeutic agents to study and treat AD.

Acknowledgments This work is supported by the National Natural Science Foundation of China (grant numbers 81270423 and 81471296) for Y.-J.W. and NSERC-Discovery RGPIN 03830-2014, Mitacs-Canada, and Early Researcher Award from the Ministry of Research and Innovation, Government of Ontario, Canada, for P.P.N.R.

Conflict of interests The authors declare no financial or other conflicts of interests.

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