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Polyphenols as Therapeutic Molecules in Alzheimer's Disease Through Modulating Amyloid Pathways

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Abstract Alzheimer's disease (AD) is a complex and multifactorial neurodegenerative condition. The complex pathology of this disease includes oxidative stress, metal deposition, formation of aggregates of amyloid and tau, enhanced immune responses, and disturbances in cholinesterase. Drugs targeted toward reduction of amyloidal load have been discovered, but there is no effective pharmacological treatment for combating the disease so far. Natural products have become an important avenue for drug discovery research. Polyphenols are natural products that have been shown to be effective in the modulation of the type of neurodegenerative changes seen in AD, suggesting a possible therapeutic role. The present review focuses on the chemistry of polyphenols and their role in modulating amyloid precursor protein (APP) processing. We also provide new hypotheses on how these therapeutic molecules may modulate APP processing, prevent Aβ aggregation, and favor disruption of preformed fibrils. Finally, the role of polyphenols in modulating Alzheimer's pathology is discussed.

Keywords Alzheimer's disease · Polyphenols · α-Secretase activator · β-Secretase inhibitor · γ-Secretase inhibitor · Aβ aggregation · Amyloid fibril disaggregation · Molecular mechanisms · Structure–activity relationships

Introduction

Neurodegenerative disease occurs as a result of changes in the native conformation of proteins, followed by accumulation of these misfolded amyloidogenic proteins in the central nervous system, which in turn causes progressive neurological impairment and neuronal dysfunction [1, 2]. This is the molecular basis of the most devastating neurodegenerative diseases known to date such as Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS) [3–5]. AD is the most prevalent neurodegenerative condition with approximately 29 million aging people suffering from this disease—a figure that is expected to triple by 2050 [6, 7].

AD is a process in which, due to uncontrolled cleavage of amyloid precursor protein (APP) by unknown inducing factors, toxic amyloid beta fragments are generated [8–10]. AD is also characterized by amyloid fibril and phosphorylated tau aggregates and tangles [11–16]. At present, there are two major challenges in AD drug discovery: first, the non-availability of an animal model that reflects all the pathological events seen in AD human brain and, second, the lack of reliable biomarkers to detect and understand the progression of AD [17–20]. Scientists are trying to develop drugs that can simultaneously perform multiple tasks such as reducing inflammation, inhibiting β-secretase, activating α-secretase, preventing of Aβ and tau aggregation, and driving the disintegration of preformed fibrils [21, 22]. However, no perfect drug or perfect treatment of AD has been discovered so far, and many drugs have failed in recent clinical trials [17].

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Consequently, research has begun to focus on natural products as alternatives in the treatment of AD [23]. For example, the water extract of the leaves of *Caesalpinia crista* has been shown to prevent Aβ aggregation from monomers and disintegrated preformed Aβ fibril; *Centella asiatica* prevents synuclein aggregation [24, 25]; *Ginkgo biloba* extract has shown to inhibit the formation of oligomers [23, 26]; extracts prepared from the medicinal herb *Paeonia suffruticosa* inhibited Aβ fibril formation and also de-stabilized the preformed amyloid fibril [26, 27]. The anti-amyloidogenic properties observed are attributed to the polyphenolic compounds present in the extracts. The present review focuses on the chemistry of polyphenols and the mechanisms by which polyphenols may induce changes in APP processing, reduction of Aβ load, prevention of Aβ aggregation, and disintegration of preformed fibrils. New mechanisms that explain the binding pattern of polyphenols to Aβ and modulation of APP processing by polyphenols are also proposed.

Chemistry of Polyphenol Compounds

Polyphenols (PPs) are natural compounds that are widespread in fruits, vegetables, seeds, cereals, oils, etc. [28]. More than 8,000 polyphenolic compounds have been identified in foods. These secondary metabolites provide protection to plants from ultraviolet light, defense against herbivory, and also attract pollinating insects [29, 30]. In the past, polyphenols have not been considered to have any substantial nutritional value; however, there is now an increased interest in exploring their potential as antioxidants [31–33]. Moreover, it has been proposed that polyphenolic compounds may play a role in the prevention of multiple diseases, such as atherosclerosis, cancer, type II diabetes, and cardiovascular and neurodegenerative diseases [34–37].

Polyphenols' chemical structure includes two or more phenol rings with hydroxyl groups in *ortho* or *para* positions, which are necessary for redox reactions [38]. There is a direct positive correlation between the antioxidant capacity and the number of hydroxyl groups present in the polyphenols' structure; i.e., an increase in the amount of hydroxyl groups in the polyphenol chemical structure is associated with increases in redox potential and antioxidant activity [39, 40].

Polyphenols are grouped into two main categories: flavonoids and non-flavonoid compounds (Fig. 1). Flavonoid compounds are classified into two groups: anthoxanthins (flavonol, flavanol, isoflavonoid, flavone, and flavanone) and anthocyanins, while non-flavonoid compounds include phenolic acids, stilbenes, curcuminoids, lignans, and tannins [41–43]. Polyphenols are secondary metabolites produced by enzymatic and non-enzymatic reactions. These reactions produce multiple secondary metabolites of biological importance (Fig. 2). The homodimeric enzyme type III polyketide synthase (PKS) produces a wide range of natural compounds by acetyltransferring, aromatization, cyclization, condensation, and decarboxylation [44]. PKS is involved in the biosynthesis of polyphenolic compounds in plants by decarboxylative condensation of acetyl units deriving from malonyl-CoA and thioester groups of cinnamoyl-CoA or *p*-coumaroyl-CoA [45–47]. For example, curcuminoids are formed by biotransformation catalyzed by curcuminoid synthase (CUS), while stilbenes are formed by biotransformation by stilbene synthase (STS). Chalcone synthase (CHS) catalyzes the formation of chalcone using *p*-coumaroyl-CoA and malonyl-CoA [45–47].

Flavonoid Compounds

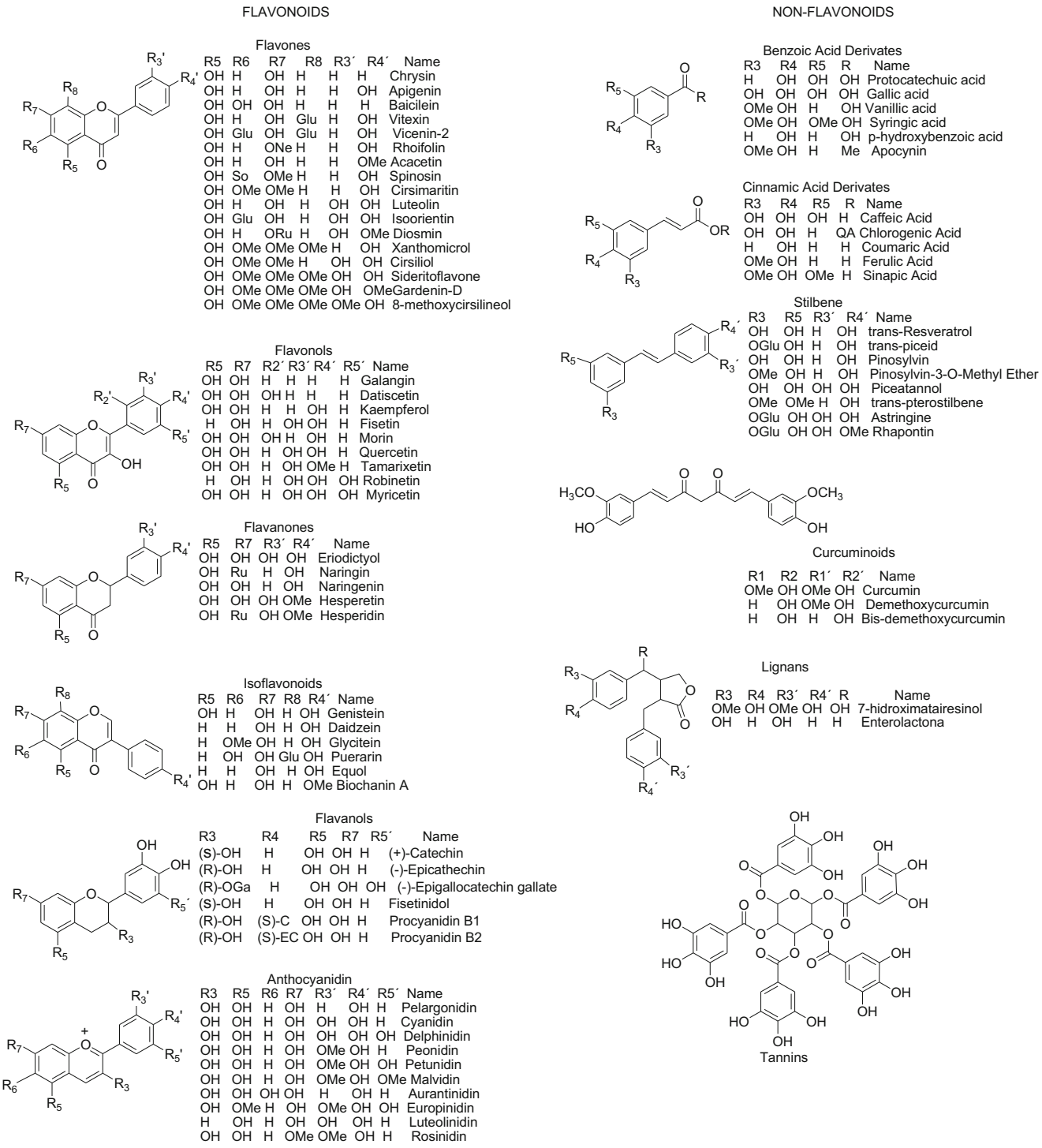
Flavonoids are the largest group of polyphenols, with more than 5,000 flavonoid compounds widely distributed in plants [48, 49]. Their basic structure consists of two aromatic rings linked through a pyran ring (Fig. 3). Depending on the oxidation state of the pyran ring, flavonoids can be classified as flavones, flavonols, flavanols, isoflavonoids, flavanones, and anthocyanins [50, 51]. Flavonoid hydroxylation occurs mainly at C_5, C_7, and C_4'. These compounds are commonly found glycosylated in plants, frequently as *O*-rhamnosyl and *O*-glucoside flavonoids, and acylation and methoxylation are less frequent [50, 52].

Flavones are characterized by the presence of a keto-pyrene group. Hydroxylation is common at C_5 [41]. Chrysin, acacetin, and baicilein are examples of common flavones found in citrus fruits, celery, and parsley [53, 54].

Flavonols possess a keto-hydroxypyrene group, which is predominantly hydroxylated at C_3, while C_5 and C_7 are frequently hydroxylated [41]. Myricetin, quercetin, and fisetin are examples of flavonols present in apples, beans, and onions [53, 54].

Flavanols contain a pyran ring hydroxylated at C_3. Flavanols can be hydroxylated at the A-ring (C_5, C_7) and B-ring (C_3', C_4', C_5') [41, 50]. Fisetinidol, catechin, and epicatechin are flavanols commonly found in berries, cocoa, tea, and onions. Proanthocyanidins or condensed tannins are oligomers of flavanols that are classified as A- and B-type proanthocyanidins [52]. B-type proanthocyanidins can be classified into two groups: procyanidins and prodelphinidins (e.g., epicatechin, catechin, and gallic ester derivate) [55].

Isoflavonoid*s* have a basic structure containing a substituted keto group on the *pyran* ring. Commonly, they are substituted at C_5, while C_6 and C_4' are methoxylated or hydroxylated. Isoflavonoids may contain a glucosyl or hydroxyl group at C_7 or C_8. Soybean is a rich source of these polyphenolic compounds [41, 50]. Flavanones also usually have a keto-pyran group usually substituted by hydroxyl groups on ring A at C_3 and C_5. Occasionally, C_7 is glycosylated or hydroxylated, while C_4' has a methoxy or hydroxy



C:catechin; **EC**: epicatechin; **Ga**: gallate; **Glu**: glucoside; **Me**: methyl; **Ne**:neohesperidose; **So**:sophorose; **Ru**:rutinose; **QA**:quinic acid.

Fig. 1 Classification of polyphenols. Polyphenols are divided into two main groups: flavonoids and non-flavonoids. Flavonoids are classified into flavones, flavonols, flavanols, flavanones, isoflavonoids, and anthocyanins. Non-flavonoids include phenolic acids, stilbenes, lignans, curcuminoids, and tannins

group. Eriodictyol, naringin, and hesperetin are flavanones present in citrus fruits [53]. Anthocyanins are ubiquitous water-soluble compounds that are responsible for red or blue colors in flowers and fruits and whose color changes according to the pH value [56, 57]. The molecular structure of anthocyanins is based on the 2-phenylbenzopyrylium cation

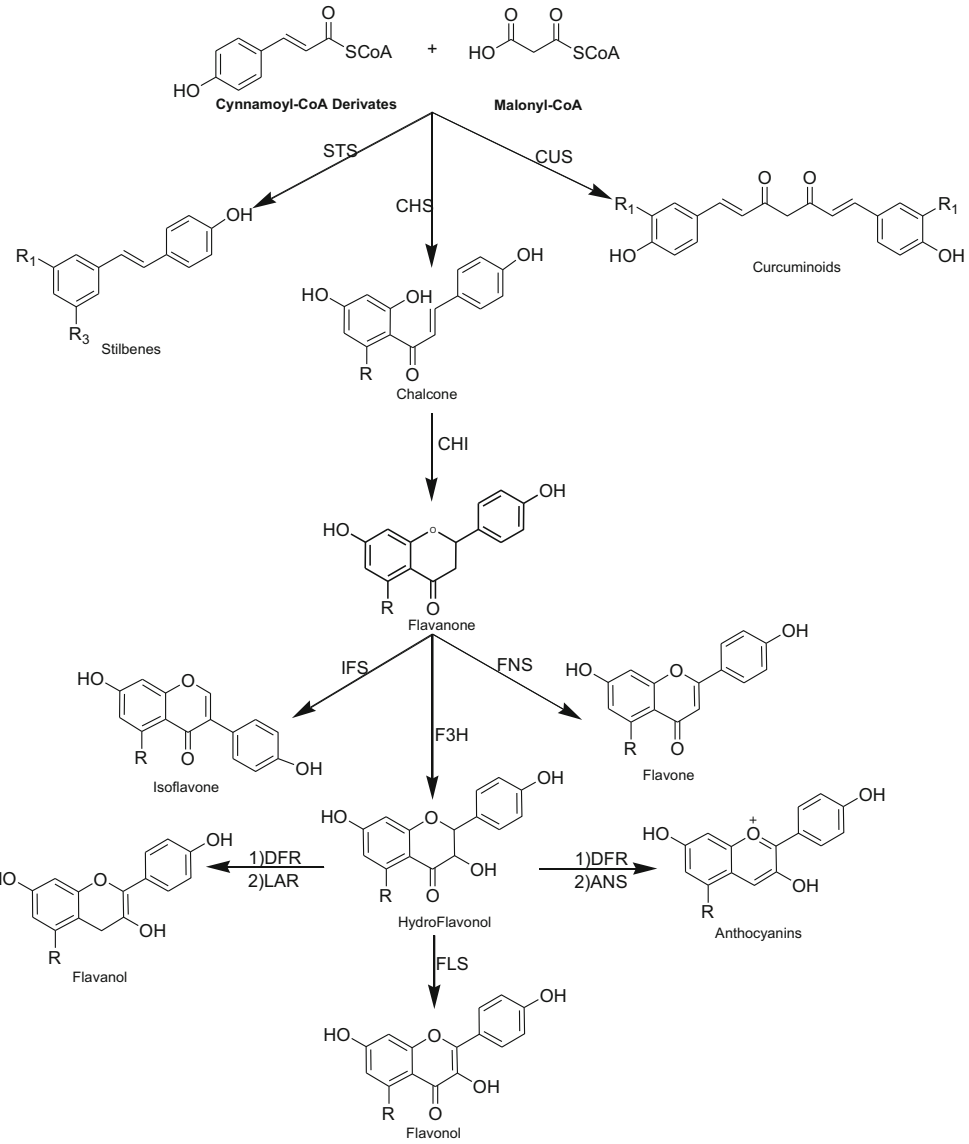


Fig. 2 Biosynthesis of polyphenols. The homodimeric enzyme type III polyketide synthase (PKS) produces a wide range of polyphenolic compounds using cinnamic acid derivatives and malonyl-CoA as substrates. Stilbene compounds are synthesized by stilbene synthase (STS) and curcuminoids by curcuminoid synthase (CUS), and flavonoid biosynthesis is initiated by chalcone synthase (CHS)

(also named flavylium) [58]. Glucose, rhamnose, arabinose, and galactose are the most common sugars found forming glycosides in anthocyanins [59]. The aglycones of anthocyanins are known as anthocyanidins, which do not exist in nature and are unstable water compounds [60]. These structures perform unique biological functions like antioxidant, anti-inflammatory, and anti-aggregation activities [61].

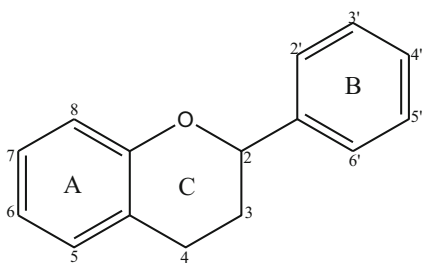


Fig. 3 Basic structure of flavonoids. Flavonoids have two aromatic rings (*A* and *B*) and a pyran ring (*C*), which classify the flavonoids into flavone, flavanol, flavonol, isoflavonoid, and anthocyanin

Non-Flavonoids

Among the non-flavonoid polyphenols are phenolic acids, stilbenes, curcuminoids, lignans and tannins, which are proven neuroprotectors. *Phenolic acids* are the simplest polyphenols found in nature. There are classified into two categories, namely, hydroxybenzoic and hydroxycinnamic acid derivates [41]. Hydroxybenzoic acid derivates (C_6–C_1) bear one aromatic ring attached to a carboxylic group. Gallic acid and protocatechuic acid are hydroxybenzoic acid derivates that are found in red fruits, black radish, and onions [50]. Hydroxycinnamic acid derivates (C_6–C_3), also known as phenylpropanoids, are more common than hydroxybenzoic acids. Caffeic, *p*-coumaric, and ferulic acids are

hydroxycinnamic acid derivates present in berries, cherries, kiwis, and apples. These polyphenolic compounds can be glycosylated or can be found forming esters with quinic acid, shikimic acid, or tartaric acid. *Stilbenes* are formed in nature through the phenylpropanoid pathway. These compounds have two aromatic rings connected through a double bond (C_6–C_2–C_6). The widely known polyphenolic compound resveratrol is a stilbene found in red grapes [50]. *Curcuminoids* [1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione] are phenolic compounds isolated from *Curcuma longa* (curcumin) [50]. *Lignans* have two phenylpropane units (C_6–C_3–C_3–C_6) bound together through β–β′ bonds. Examples include secoisolariciresinol, which is found in sesame and pumpkin seeds [50]. *Tannins* are complex polymers of high molecular weight (>30,000 Da) classified as hydrolizable and condensed tannins. Hydrolyzable tannins are heterogeneous polymers of phenolic acids, which are classified as gallotannins, composed of gallic acid and glycosides and ellagiotannins, constituted by ellagic acid [41].

The role of different polyphenols in modulating APP processing, as well as their anti-aggregation properties, is discussed below.

New Hypothesis on Polyphenols Modulating APP Pathway

APP is a large type-1 transmembrane multidomain protein that performs multiple cellular activities. APP_{695}, APP_{751}, and APP_{770} are the most frequently expressed isoforms in the brain [8, 62]. APP is catabolized by secretases (α, β, and γ), forming non-amyloidal and/or amyloid-derived products [61, 63]. In the non-amyloidal pathway, α-secretase cleaves APP at Lys 687, producing sAPPα and a C-terminal fragment of 83 aa residues (CTFα), which are further cleaved by γ-secretase leading to the formation of $Aβ_{17–42}$ (also known as protein 3 (p3)), and APP intracellular domain (AICD) [64]. In the amyloidal pathway, β-secretase cleaves APP at Met 671, releasing a fragment of the secreted amyloid precursor protein beta (sAPPβ), and a C-terminal fragment of 99 aa residues (CTFβ). The latter is then cleaved by the enzyme γ-secretase at Val 711 and Ala 713, leading to the formation of AICD, Aβ40, and Aβ42 peptides [65–67]. Beta-site amyloid precursor protein cleaving enzyme 1 (BACE1), also known as β-secretase, is involved in the production of amyloid-β peptide [68]. β-Secretase has 501 aa residues, including a signal peptide of 21 aa residues, a proprotein domain (22–45 aa), a luminal domain (46–460 aa), a transmembrane domain (17 aa), and a cytosolic carboxyl domain of 24 aa [68]. A BACE1 homolog, named BACE2, cleaves APP into a short peptide. However, BACE2 is present in small quantities in the brain, and so, this enzyme is probably not crucial in the formation of Aβ peptide. γ-Secretase is a heterotetrameric membrane-embedded aspartyl protease consisting of four subunits: nicastrin, presenilin, anterior pharynx, and presenilin enhancer 2 [69–71]. When α- or β-secretase cannot cleave APP, γ-secretase cleaves it, forming the soluble amyloid precursor protein γ (sAPPγ) and AICD [72]. Finding drugs that target APP processing is complex and challenging due to the multiple functional enzymes and substrates involved [17].

Polyphenols are powerful anti-amyloidogenic compounds due to physicochemical features such as the presence of aromatic rings, molecular planarity, capacity to form hydrogen bonds, the presence of an internal double bond, and molecular weights below 500 g/mol, which allow for potential inhibition of APP pathways (Fig. 4) that, in turn, reduces amyloid load [73–76].

Polyphenols as Activators of α-Secretase

Several members of the a disintegrin and metalloproteinase (ADAM) family have been proposed as physiologically active α-secretases, namely: ADAM9, ADAM10, and ADAM17. It has been demonstrated that ADAM10 has the highest α-secretase activity "in vivo" [77–79]. Moreover, it has been suggested that the upregulation of ADAM10 could be a potential therapeutic target for the treatment of Alzheimer's disease. ADAM10 has a potential neuroprotective role because it promotes the non-amyloidogenic pathway [80]. This enzyme is activated by removal of the prodomain, which is probably promoted by the action of proprotein convertases [81–84]. Phlorotannins and epigallocatechin-3-gallate (EGCG) have been shown to increase the overexpression of sAPPα through activation of α-secretase favoring neuroprotection [85–87]. Other polyphenols such as curcumin induce ADAM10 activation, whereas curcumin–amino acid conjugates favor the overexpression of sAPPα. Other esters found in nature such as phorbol 12,13-dibutyrate (PDBU) and phorbol 12-myristate 13-acetate (PMA) also increase the overexpression of sAPPα by activation of α-secretase [88]. Based on this similarity, we propose a hypothetical structure–activity relationship by which a covalent interaction between the ester group of EGCG and curcumin–amino acid conjugates and the enzyme prodomain promote the release of the active site, allowing the cleavage of APP to form sAPPα fragments (Fig. 5a) [89, 90].

Polyphenols as Inhibitors of β-Secretase

The amino acids Asp32, Asp228, and two water molecules, all located in the catalytic binding site of BACE1, are essential for catalytic activity [91]. One of these water molecules participates in enzymatic proteolysis, while the second water molecule is key for stabilizing a tetrahedral intermediate that is essential for protein cleavage [92]. Computational modeling studies indicate that Asp32 is protonated, whereas Asp228 is not [91]. Proteolytic BACE 1 activity is initiated through a nucleophilic attack by a water molecule on the carbonyl group of the peptide bond

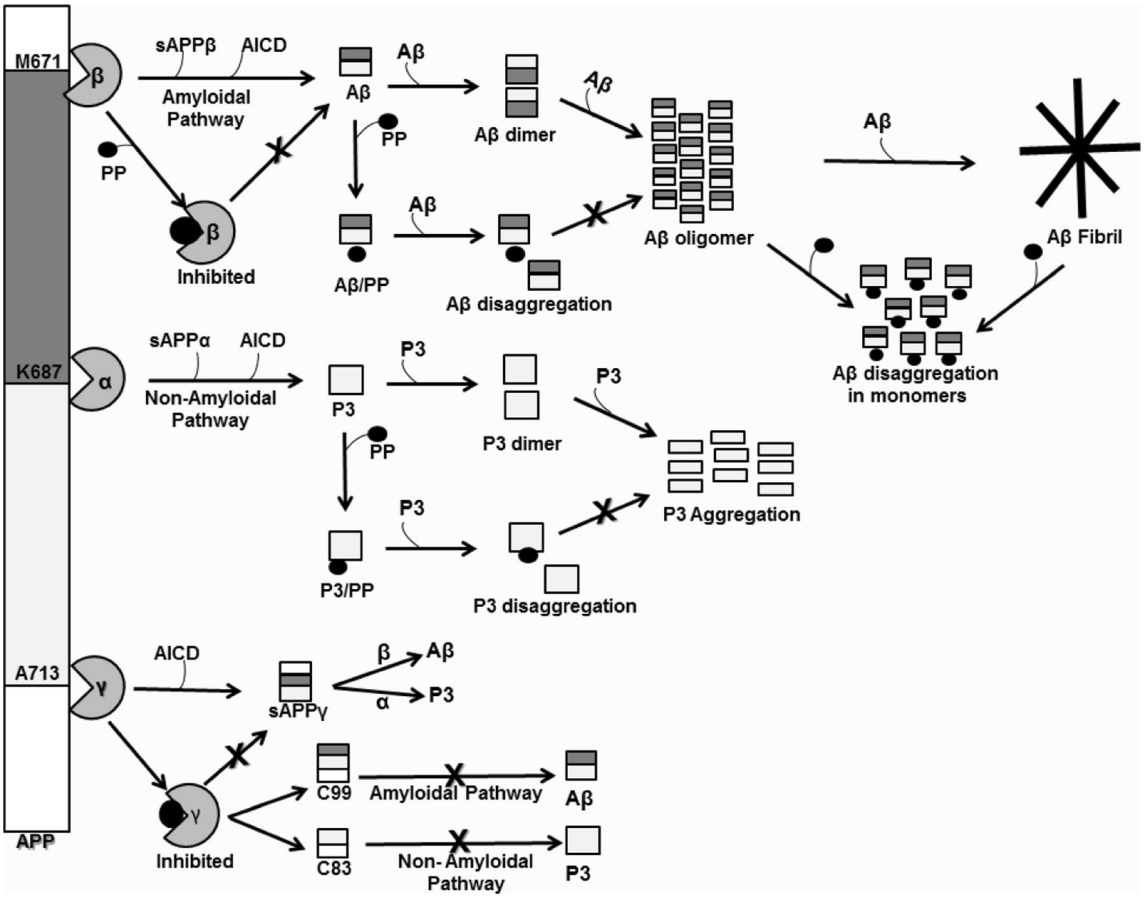


Fig. 4 A hypothesis on the role of polyphenols in modulating the amyloid precursor protein processing: α-, β-, and γ-secretases are involved in amyloid precursor protein (APP) processing. (i) Amyloidal pathway: β-secretase cleaves APP to produce soluble amyloid precursor protein β (sAPPβ) and a C-terminal 99 fragment, which is then cleaved by γ-secretase to generate Aβ peptides. Amyloid beta fibrils are formed by aggregation of these amyloid peptides. (ii) Non-amyloidal pathway: tα-secretase cleaves APP to form the soluble amyloid precursor protein α (sAPPα) and a C83 fragment. The γ-secretase cleaves this fragment to produce non-amyloidogenic $A\beta_{17–43}$ peptides. Polyphenols are potential activators of α-secretase and inhibitors of β- and γ-secretase, leading to reduction of amyloid fibril deposition in the brain

[93]. Inhibition of BACE1 represents a potential therapeutic target in AD treatment as it decreases Aβ load. Several peptides are known to inhibit beta secretase, yet small molecules, namely isophthalamides, have shown higher inhibitory effect upon BACE1 [94]. Myricetin is a potential BACE1 inhibitor [95]. We propose a mechanism that explains the role of polyphenol-induced inhibition through the displacement of a water molecule, which then participates in a hydrogen bonding network with Asp32 and Asp228 that is essential for BACE1 proteolytic activity. It is very probable that flavonols having a myricetin-like chemical structure cause inhibition of BACE1 following this same mechanism (Fig. 5b) [96].

Polyphenols as Inhibitors of γ-Secretase

Presenilin I (PS1) protein is a member of the aspartic protease family implicated in the regulation of intramembrane proteolysis [66, 70]. PS1 has been identified as the catalytic subunit of the γ-secretase complex. This protein is composed of nine transmembrane domains, where domains 6 and 7 form the catalytic site. Mutations in PS1 have been linked to familial Alzheimer's disease (FAD). Therefore, PS1 is a potential target in the design of drugs against AD [71, 97]. Two aspartyl groups (Asp257 and Asp385) opposed to each other in the active site and are required for the catalytic activity of PS1. One of these aspartates is deprotonated and acts as a base, activating a water molecule present in the catalytic site. The other aspartate donates a proton to the carbonyl group of the substrate, following an acid–base mechanism [97]. We propose that polyphenols that can occupy the active site of γ-secretase (thus displacing the water molecule required by the enzyme for catalysis) would disable the enzyme and reduce Aβ formation [97] (Fig. 5c).

Structure–Activity Relationship of Polyphenols on Their Aβ Anti-Aggregation Activity

$A\beta_{42}$ aggregation is a hallmark of AD pathology; therefore, inhibition of $A\beta_{42}$ aggregation is a key factor in drug discovery.

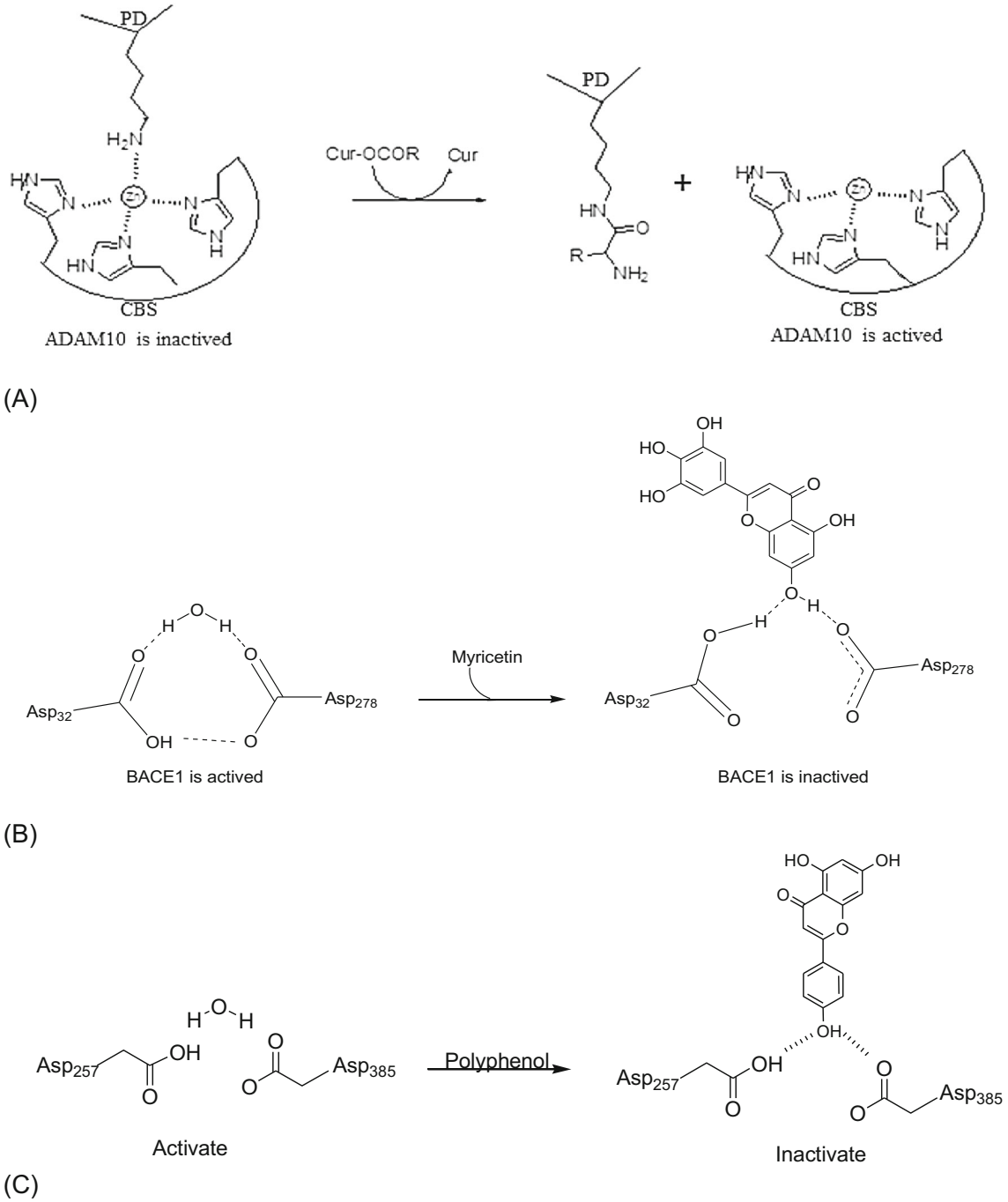


Fig. 5 Binding mechanisms involved in the activation or inhibition of secretases by polyphenols. **a** Curcuminoid esters activate α-secretase by effectively releasing the prodomain. **b** Polyphenol occupies the position of a water molecule essential for β-secretase proteolytic activity, leading to enzyme inhibition. **c** Polyphenols might inhibit γ-secretase by displacing the water molecule between Asp 257 and Asp 385

$A\beta_{42}$ aggregation biology is a multifold step, where monomers form oligomers, protofibrils, and matured fibrils. Drug discovery efforts are focused on preventing the formation of either oligomers or fibrils. There are also studies focusing on disintegration of preformed fibrils [23–27]. However, there are limited studies exploring how drugs bind to $A\beta_{42}$ and prevent fibril formation [23–27, 98–102]. The primary sequence of the $A\beta_{42}$ peptide is H_2N-DAEFRHDSGYEVHHQKL-VFFAEDVGSNKGAIIGLMVGGVVIA-CO_2H [103–105]. More than 50 % of the amino acids in this peptide are hydrophobic residues [106]. It has been suggested that the hydrophobic core KLVFF is essential for fibrillogenesis [107–109]. Aβ peptide may be considered as a molecule with two faces (upper and lower), which allow it to self-assemble and to form oligomers and matured fibrils [98–101]. Wang et al. have identified significant binding sites on the $A\beta_{42}$ peptide structure: F4-H6,

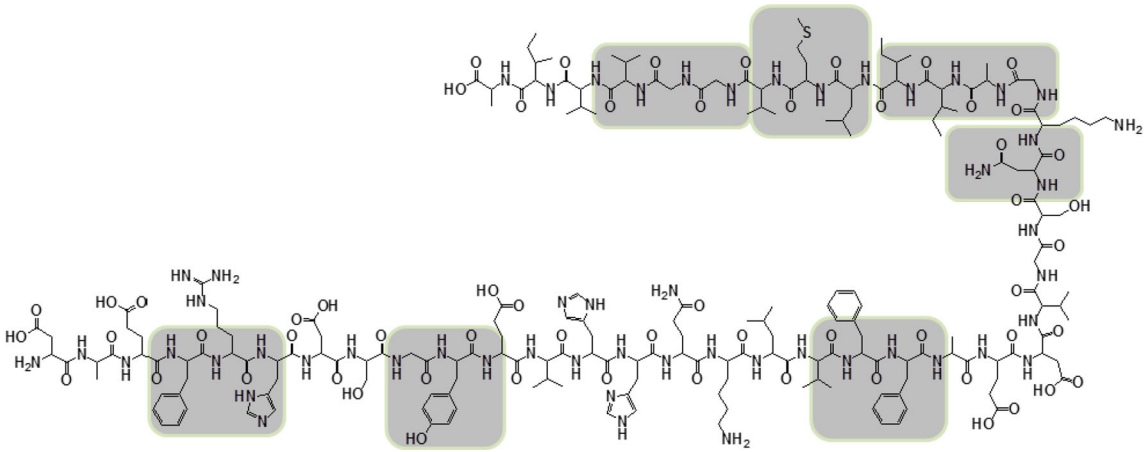


Fig. 6 Proposed binding sites of polyphenols on amyloid beta peptides. Seven binding sites have been proposed in the amyloid beta peptide (highlighted amino acids residues). The three first sites are characterized by having aromatic rings, which may be involved in molecular recognition and self-assembly. The sites 4 to 7 form a hydrophobic groove region in the amyloid fibril

Y10, F20, N27, I31-M35, M35, and M35 to V39 for molecules like tanshinones [102]. Based on these data, we propose a model that identifies proposed binding sites for polyphenols on amyloid beta peptides (Fig. 6) [102].

Aβ fibrillization is a multistep process, which begins with the formation of Aβ oligomers constituted by 24 monomers [110–113]. The toxic spherical oligomers are considered an intermediate into fibril formation and are 3–10 nm in size. Aβ fibrils are characterized by highly stable crossed β-sheet structures at 4.75 and 9.8–10.6 Å [114–117]. Amyloid fibril formation depends on the increase in the concentration of $A\beta_{42}$ peptide, low pH, the time of incubation, and the length of the carboxyl chain [118]. Studies have indicated that hydrophobic forces, aromatic stacking, and electrostatic interactions stabilize the Aβ structure [119, 120]. The main physicochemical properties of molecules with the potential to inhibit amyloidal fibril formation might be due to the presence of aromatic rings in their chemical structure and the ability to form non-covalent interactions with amino acids residues of the Aβ peptide sequence [73, 74]. Moreover, the planarity of the inhibitor is essential for increasing surface contact with Aβ peptides [75]. Most polyphenols have more than two aromatic rings essential for π–π stacking interactions with hydrophobic amino acid residues of Aβ (Tyr, Phe) and at least three hydroxyl groups that form hydrogen bonds with hydrophilic amino acid residues of Aβ (His6, Ser8, Tyr10, His14, Lys16) [121–123]. The resonance structure of polyphenols provides enough planarity to penetrate the Aβ fibril hydrophobic grove, thus disturbing the fibril structure [124].

Polyphenolic compounds such as resveratrol, curcumin, and myricetin have demonstrated anti-Aβ aggregation properties [111, 125–130]. The differences observed in the anti-aggregation activity among polyphenols are related to their chemical structure. Generally, non-flavonoids (tannins>stilbenes>curcuminoids) show higher anti-amylodogenic activity than flavonoids (flavonols>anthocyanins>flavanol>

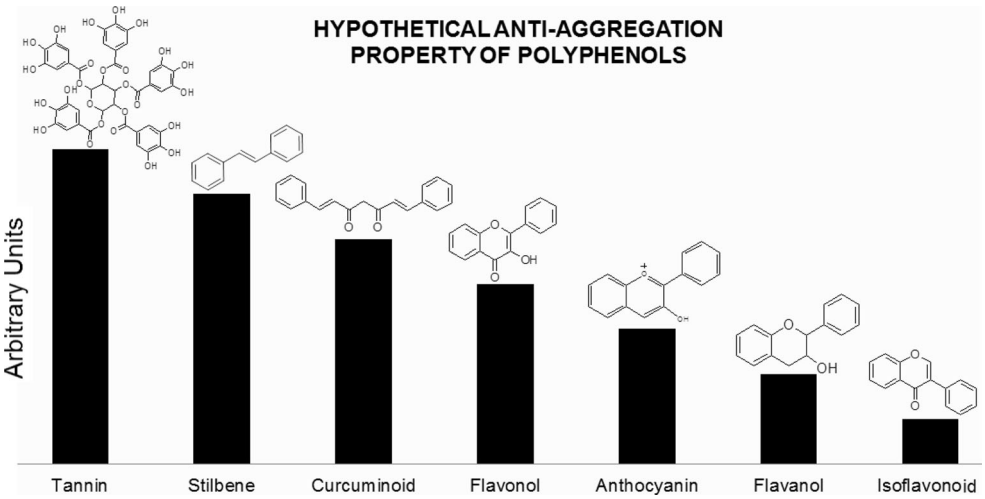


Fig. 7 Hypothetical model to understand the anti-aggregation activity of polyphenols. Polyphenols have demonstrated anti-aggregation activity. Non-flavonoids showed higher anti-aggregation activity than flavonoids. We propose a relationship between polyphenol structure and anti-aggregation activity, in which polyphenols with more aromatic rings, planarity, and hydroxyl and keto groups might have the largest inhibition activity

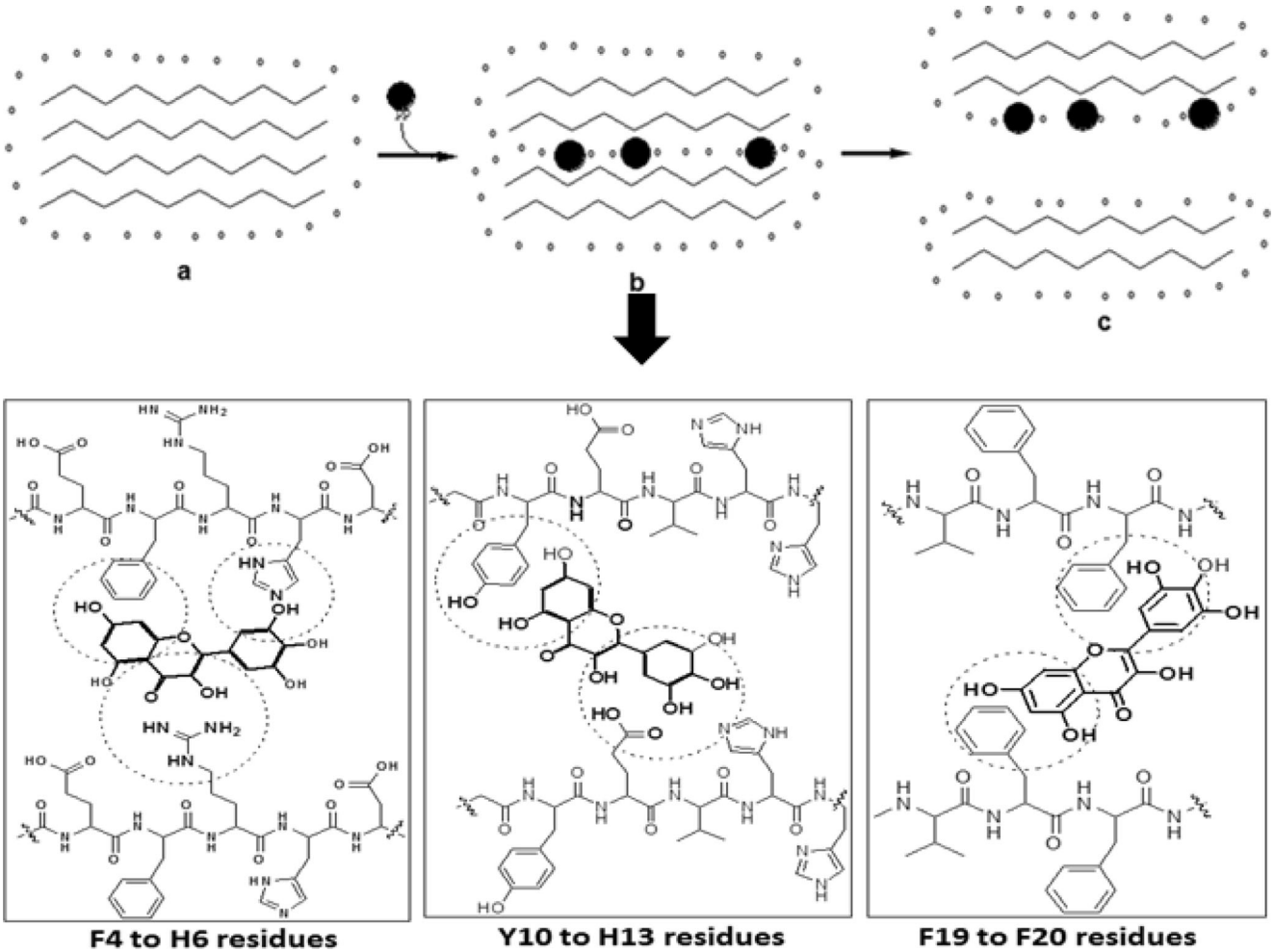


Fig. 8 Proposed mechanisms for explaining the disintegration of preformed amyloid beta fibril by polyphenols. **a** Amyloid fibrils are stabilized through hydrophobic effects established among Aβ peptides. **b** Polyphenols inside the amyloid fibril groove might establish aromatic and hydrogen bond interactions with amino acids residues located within this molecular region, inducing fibril disaggregation. **c** Polyphenol compounds may disrupt preformed amyloid fibril structure by reducing the hydrophobic effect

isoflavonoid) [131, 132]. Nevertheless, no clear mechanisms have been proposed so far to explain how polyphenols prevent Aβ aggregation. Therefore, we suggest hypothetical structure–activity relationships (Fig. 7) based on structural comparisons of polyphenols to explain how polyphenolic compounds prevent Aβ aggregation [133, 134].

Isoflavonoids generally show lower anti-aggregation activity than other flavonoids. Structure–activity relationships of isoflavonoids and other flavonoids suggest that the aromatic B ring at C2 is essential for decreasing amyloid fibril formation due to favorable non-covalent interactions between polyphenols and amino acids of the Aβ peptide sequence [135].

Flavanols possess more anti-amyloidogenic activity than isoflavonoids because they contain more hydroxyl groups able to form hydrogen bonds with Aβ peptides. Nevertheless, flavanols have two chiral centers (C_2, C_3) that may diminish molecular planarity [136]. Furthermore, these compounds lack the presence of a keto group at C4 in the C ring, leading to less non-covalent interactions with Aβ peptides. Both physicochemical features have negative effects on the inhibition of fibril formation [132, 137].

Anthocyanins are characterized by having a pseudo aromatic ring C that increases their structural planarity and promotes amyloid fibril disruption due to effective incorporation of anthocyanins inside the amyloid beta fibril groove. Curcuminoids are more hydrophobic than flavonoids. This physicochemical property might enhance their affinity for binding with the hydrophobic core of Aβ fibril, resulting in an increased anti-amyloidal activity [132]. Stilbenes have more hydroxyl groups in their chemical structure than curcuminoids, which may explain the strong anti-aggregation activity observed for these polyphenols [137, 138]. Tannins are complex polyphenols having the highest number of hydroxyl groups among polyphenolic compounds and therefore the strongest anti-aggregation activity [139–142]. Nevertheless, their large molecular weight reduces their suitability as a therapeutic drug [76].

The possible mechanisms used by polyphenols to destabilize preformed fibrils remain unclear [143]. When polyphenols get inside the hydrophobic groove of Aβ fibril, their aromatic rings disrupt the organization of the fibril due to attraction and repulsion between the polyphenol and the Aβ peptide [144, 145]. We suggest that these interactions may lead to conformational changes that might favor widening of the amyloid fibril groove through reduction of the hydrophobic effect (a major driving force that stabilizes the fibril structure), leading to a disaggregation of amyloid fibril (Fig. 8) [124].

Conclusion

The understanding of polyphenol bioavailability and health benefits is still not so clear. However, population studies on polyphenols and memory have shown that polyphenols contribute to a healthy brain. There have been studies showing that some polyphenols can cross the blood–brain barrier and confer neuroprotection. A lot of information is available on the influence of polyphenols on the differential expressions of genes involved in inflammation, apoptosis, and tumor necrosis. The current challenge in polyphenol research is related to their bioavailability at pharmacological concentrations. Some polyphenols appear to have pharmacological capabilities against cancers, metabolic disorders, and memory, but we still need to understand the delivery mechanisms of these compounds. The major challenge is to bring blood polyphenol concentrations up to the levels required for pharmacological action [146].

It is a challenge to cover all of the possible molecular mechanisms utilized by any drug in the treatment of AD, as this disease has multiple pathological events. Polyphenols have attracted research interest recently due to their multiple effects such as inhibition of Aβ, metal chelation, and prevention of mitochondrial dysfunction and apoptosis, as well as their antioxidant and anti-inflammatory properties. Although there are no clear mechanisms described so far that fully explain the role of polyphenols in the treatment of AD, we have presented some well-founded hypotheses that associate the physicochemical properties of polyphenols with their possible role in α-secretase activation, β- and γ-secretase inhibition, disaggregation of Aβ fibrils, and anti-Aβ aggregation. To the best of our knowledge, this review thus provides some novel avenues for future research.

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