

Review

Polyphenol-Peptide Interactions in Mitigation of Alzheimer's Disease: Role of Biosurface-Induced Aggregation.

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Abstract: Alzheimer's disease (AD) is the most common age-related neurodegenerative disorder, responsible for nearly two-thirds of all dementia cases. In this review, we report the potential AD treatment strategies focusing on natural polyphenol molecules (green chemistry) and more specifically on the inhibition of polyphenol-induced amyloid aggregation/disaggregation pathways: in bulk and on biosurfaces. We discuss how these pathways can potentially alter the structure at the early stages of AD, hence delaying the aggregation of A β and tau. We also discuss multidisciplinary approaches, combining experimental and modelling methods, that can better characterize the biochemical and biophysical interactions between proteins and phenolic ligands. In addition to the surface-induced aggregation, which can occur on surfaces where protein can interact with other proteins and polyphenols, we suggest a new concept referred as "confinement stability". Here, on the contrary, the adsorption of A β and tau on biosurfaces other than A β - and tau-fibrils, e.g. red blood cells (RBCs), can lead to confinement stability that minimizes the aggregation of A β and tau. Overall, these mechanisms may participate directly or indirectly in mitigating neurodegenerative diseases, by preventing protein self-association, slowing down the aggregation processes, and delaying the progression of AD.

Keywords: Amyloid; Blood cells; Computer simulation; Polyphenols; Tau

1 **1. Introduction**

2 Alzheimer's disease (AD) is the most common age-related neurodegenerative disorder,
3 responsible for nearly two-thirds of all dementia cases [1, 2] including Lewy body dementia, vascular
4 dementia and frontotemporal dementia (FTD) [3, 4]. The prevalence of AD is about 5-10% above the
5 age of 60 years but increases up to 40-50% above the age 85 years [5]. With the ageing of the
6 population [6], dementia affects nearly 50 million people worldwide, and is predicted to increase to
7 152 million by 2050 [7]. The estimated annual healthcare cost is US \$1trillion, which could double by
8 2030 [7].

9 The multifactorial disorders of AD, considering genetic and non-genetic components, are clinically
10 characterized by memory dysfunction, loss of lexical access, spatial and temporal disorientation and
11 impairment of judgement. Although, the molecular mechanisms of AD have not been fully elucidated
12 yet, compelling evidence indicates that abnormal proteins accumulation in the brain, such as the
13 intracellular aggregation of the tau [8-10] and extracellular deposition of amyloid beta (A β) [11, 12]
14 leads to neuronal loss [13]. However, the heterogeneous nature of neurodegenerative disorders
15 increases the challenges to understand the underlying mechanisms from the initial phases to the
16 progression of AD. Over the years, several pathways have been studied including the A β cascade and
17 deposition, abnormal tau aggregation, oxidative stress, mitochondrial dysfunctions, lysosomal
18 alterations, neuroinflammation, and metabolic disorders where all of these converge to
19 neurodegeneration (Figure 1).

20 *1.1 The amyloid- β pathway*

21 Since 1991, the amyloid-cascade hypothesis has provided the main framework to understand the
22 pathogenesis of AD [14, 15]. The basis for this hypothesis was the discovery of autosomal dominant
23 mutations in three genes — APP, PSEN1 and PSEN2 (the latter two encoding presenilin 1 and 2,
24 respectively) — that induce pathogenic A β aggregation into neuritic plaques [14, 15]. The amyloid
25 precursor protein (APP), a type I transmembrane protein, contains a large extracellular domain [16].
26 In familial AD with APP mutations, the amyloid cascade leads to early onset of cognitive deficits and
27 dementia, likely through complex age-dependent cellular and molecular changes, including the
28 spreading and deposition of neurofibrillary tangles (NFTs). Although mutations in the above three
29 genes do not occur in sporadic AD, similar neuropathological changes in A β and tau were observed in
30 both familial and sporadic AD [17-19].

31 Over the years, the amyloid-cascade hypothesis involved into an integrative model that provides
32 a general framing for other disease mechanisms, e.g., immunoreactivity, microgliosis, mitochondrial
33 dysfunction, oxidative stress, and dysregulation of protein homeostasis [20, 21].

34 *1.2. The amyloid- β and Tau integrative pathways*

35 It is now thought that A β and tau pathologies can follow both independent and dependent
36 pathways leading to AD. A β preferentially accumulates in brain regions with high metabolic demand
37 (such as association cortices) and spreads from neocortex to allocortex to brainstem, eventually
38 reaching the cerebellum [22-24]. Tau pathology, by contrast, first becomes evident in the
39 (trans)entorhinal cortex from which it spreads to limbic areas, and from there to the neocortex [25-
40 28]. The finding that A β and tau pathologies initially start in different brain regions, referred to as the
41 'spatial paradox', argues against the idea that tau pathology is driven by amyloid pathology occurring
42 in the same local brain area. A β and tau pathologies also follow distinct temporal sequences because
43 A β in the neocortex is already present 10–20 years before the emergence of clinical AD symptoms and
44 the rate of A β accumulation attenuates during the clinical stage of AD [29]. In addition, the extent and

1 locations of A β deposition are only modestly correlated with the brain areas affected by
2 neurodegeneration [30, 31]. Both spatially and temporally, tau pathology correlates much more
3 strongly with neurodegeneration and cognitive impairment than A β pathology. Increased tau PET
4 signal is associated with worse cognitive performance in both cognitively normal individuals and
5 patients with clinical AD [26, 27, 32, 33]. The spread of tau pathology was associated with a specific
6 gene-expression profile of 'axon-related' genes, whereas the spread of A β was linked to a different
7 profile of 'dendrite-related' genes. A third subset of 'lipid metabolism-related' genes was linked to
8 increased spread of both A β and tau pathology [34].

9 Learning, memory and cognitive deficits characterize AD patients, whereas memory deficits are a
10 hallmark of amnesic mild cognitive impairment (aMCI). These altered functions largely originate from
11 synaptic dysfunction involving altered synaptic proteomes [35, 36] with the particular contribution of
12 A β 42 oligomers [35, 37]. These oligomers cause oxidative damage to synaptic membranes [38],
13 suggesting the relation between oligomer-induced oxidative damage and synaptic dysfunction.

14 *1.3. Role of the amyloid- β oligomers*

15 Many oligomeric A β species have been described [39]. Large oligomers of A β 42 are relatively less
16 toxic whereas small A β 42 oligomers (e.g. dimers or trimers that easily enter lipid bilayers) appear
17 highly toxic to synapses [40]. Thus, in the absence of amyloid plaques, soluble A β oligomers from AD
18 brains have been showed to impair hippocampal synaptic plasticity, decrease synapses, induce tau
19 hyperphosphorylation and neuritic dystrophy, activate microglial inflammation, and impair memory in
20 normal adult rodents [40]. Together, the soluble fraction of high molecular weight (HMW) oligomeric
21 A β s are far less bioactive than the smaller oligomers in AD brain. The composition of A β plaques is both
22 fibrillar and soluble HMW oligomeric A β s. Therefore, it is important to target diffusible A β species that
23 are highly bioactive in AD brain. Thus, the neutralization of the toxicity of oligomeric A β species was
24 suggested as a chronic therapy for AD [41, 42].

25 *1.4. Amyloid- β -targeted therapies*

26 To date, there is no approved drugs that can either revert or cure the AD. The amyloid cascade
27 hypothesis has also guided most drug discovery efforts in both familial and sporadic AD, where the
28 objective was the removal of various forms of cerebral A β . Unfortunately, if A β -targeted therapies
29 tested in phase III clinical trials (bapineuzumab, gantenerumab, solanezumab, crenezumab,
30 lanabecestat, atabecestat, verubecestat and elenbecestat) [43] can effectively reduce A β load in AD
31 brains, they were unsuccessful in slowing cognitive decline either with mild cognitive impairment or
32 AD patients. In addition, two phase III clinical trials of A β -targeted therapy, aducanumab, were halted
33 in March 2019 [44]. Interestingly, in one of the two trials, cognitive decline was attenuated in patients
34 receiving high dose aducanumab, [44]. However, Alzheimer's drug candidate aducanumab took a
35 beating from FDA advisors (Science, Nov. 6, 2020) and the FDA's decision is expected by March 2021
36 [45].

37 The lack of beneficial effects on cognitive outcome from these trials could be due to different
38 reasons such as the timing of the interventions, as the studies involved patients in clinically advanced
39 stages of AD, and insufficient dosing or the wrong A β species being targeted [46]. Alternatively, the
40 failure of these trials could indicate that removing A β from the brain is not sufficient to halt cognitive
41 decline suggesting that tau pathology, tau-mediated neurodegeneration and other mechanisms in AD
42 are driven partially by A β pathways. Most of the unsuccessful therapeutic approaches for AD had
43 focused on A β or Tau pathways. Interestingly, Hammond et al. [47] suggested that AD treatments may
44 also need to be disease stage-oriented with A β and tau as targets in early AD and glucose metabolism
45 as a target in later AD. Recently, the EU-US Clinical Trials on Alzheimer's Disease (CTAD) Task Force

1 reported that effective treatments should include new biomarkers intervening in early stages of AD,
2 and of combination therapies [44]. This lead to the diversification of the development of the drug
3 portfolio.

4 *1.5. Protection against A β by polyphenols*

5 In this regard, several polyphenols have been investigated to promote neuroprotection by
6 targeting A β oligomers and attenuated A β -induced-ROS production, restore the A β -induced reduction
7 of antioxidants activities or mitochondrial dysfunctions (Figure 1) [48-51]. Numerous flavonoids can
8 interact and destabilize A β peptide structures, function of ligand:A β molar ratio [52]. Most polyphenols
9 that are A β -aggregation inhibitors share a catechol moiety, also related to anti-oxidative stress, such
10 as: (+)-taxifolin, myricetin, quercetin, (+)-catechin, epigallocatechin gallate (EGCG), anthocyanins [53],
11 OH-tyrosol, tyrosol [54-57] and rosmarinic acid or grape-derived polyphenols [58-61]. As a result, these
12 compounds can efficiently destabilize the β -sheet structures of A β and prevent the elongation of A β
13 oligomers.

14 Interestingly, some antioxidant polyphenols, such as resveratrol or quercetin-3-O-glucoside
15 [62], are able to enter the brain to a limited extent and have shown promise for AD treatment [63].
16 Another mechanism by which polyphenols could exert protective properties is by generation of a
17 hormetic response to their use [64-66], i.e. they generate a mild oxidative stress that the body tries to
18 mitigate by upregulating protective genes. This often leads to increases in the levels of antioxidants
19 such as glutathione and HO-1, mediated by activation of the transcription factor nuclear factor
20 erythroid 2-related factor 2 (Nrf2) [66, 67] (Figure 1).

21 Among the 560 anthocyanins (ACNs) identified in nature, the common anthocyanidin
22 aglycones, e.g., pelargonidin, cyanidin, delphinidin, peonidin, petunidin, and malvidin, can form
23 covalent conjugates with sugars and organic acids to generate a plethora of ACNs. Some ACNs have
24 the ability to cross the blood brain barrier and reach the brain [68, 69], particularly the hippocampus
25 [70-73]. The type and concentration of ACNs differ widely among different fruits and vegetables,
26 ranging from 1.4 mg/g to 800 mg/g of dry weight [74]. Youdim et al. [75] reported the citrus flavonoids,
27 hesperetin, naringenin and their relevant *in vivo* metabolites, as well as the dietary ACNs and *in vivo*
28 forms, cyanidin-3-rutinoside and pelargonidin-3-glucoside, are taken up by two brain endothelial cell
29 lines from mouse (b.END5) and rat (RBE4).

30 In this review, we first discussed the biochemical aspects of A β and tau which are relevant to
31 β -amyloidopathy and tauopathy. We then reported the potential of AD treatment strategies focusing
32 on natural polyphenol molecules (green chemistry) and specifically on the inhibition of polyphenol-
33 induced amyloid and/or tau aggregation or disaggregation pathways. We discussed how polyphenols
34 can potentially alter the structure and/or delaying A β and tau self-association at the very early stage
35 of AD, hence, potentially playing a key role in the progression of neurodegenerative disorders. In
36 addition, we suggest a new concept, referred as “confinement stability”, where the adsorption of A β
37 and tau on biosurfaces other than A β - and tau-fibrils, e.g. membranes, vessels, red blood cells (RBCs)
38 etc., can either lead to confinement stability or to surface-induced aggregation, depending on the
39 affinity of A β and tau to these surfaces.

40 **2. Biochemical Aspects of A β 40 and A β 42**

41 The molecular weights of A β 40 and A β 42 monomers are 4.33 and 4.51 kDa, respectively. A β 42
42 with two additional hydrophobic residues (Ile41 and Ala42) at the C-terminus, shows a greater
43 propensity to induce fibrils formation than A β 40 [76]. The predicted solubility is higher for A β 40 than
44 A β 42 being 0.4 μ M and 0.04 μ M, respectively [77], consistent with A β 42 experimental solubility of

1 0.04 μM [78]. Both A β 40 and A β 42 monomers have a hydrodynamic radius (Rh) of 0.9 ± 0.1 nm [79],
2 i.e. below the colloidal domain ($\sim 5\text{nm}$ to $5 \mu\text{m}$) [80]. The total mass of A β is estimated to 6.5 mg in
3 cortical grey matter of AD brain compared to 1.7 mg in control brains [81]. For example, an A β rate of
4 mass accumulation of 30 ng/hour is enough to place a person on the trajectory to accumulate 5mg of
5 A β in the brain over a 20-year time frame [81]. The *in vivo* fractional production and clearance rates
6 of A β in the human CNS was reported to be 7.6% per hour and 8.3% per hour, respectively
7 [82]. Importantly, A β fibrils from human brains are right-hand twisted, quite different from *in vitro*
8 fibrils [83]; this emphasizes the preferred use of human AD brains in future investigations. Additional
9 biochemical aspects of A β s can be found in Ref. [84].

10 **3. Biochemical Aspects of Tau**

11 In the perspective of understanding tau aggregation mechanisms, the following describe some
12 biochemical and biophysical properties of tau protein implicated in AD: structures, domains,
13 phosphorylated and binding residues, solubility, ionic charge, prone to or suppression of aggregation,
14 etc.

15 The accumulation of misfolded and aggregated forms of tau protein in the brain is a
16 neuropathological hallmark of tauopathies observed in neurodegenerative diseases (NDs), including
17 AD and Pick's disease [85-87]. The microtubule-associated protein tau (MAPT), identified in mid-1970s
18 [88, 89], encodes the protein tau [90]. Tau is notably characterized by the presence of three or four
19 (according to the isoforms) imperfect repetitions of a motif of about 30 residues, known as the
20 microtubule-binding repeats (MTBRs), and where the N-terminal to the MTBR is a proline-rich region
21 (PRR) [91]. Moreover, tau can be characterized into four sections: N-terminal projection, proline-rich
22 domain, microtubule-binding domain (MBD), and a C-terminal [92]. Tau full length monomer
23 (hTau40wt(441)) has a molecular weight of 45.8 kDa, a radius of gyration (Rg) of 6.5 ± 0.3 nm and a
24 hydrodynamic radius (Rh) of 5.3 nm [93], within the colloidal domain.

25 Tau is a natively unfolded protein largely found in axons, where it serves to stabilize
26 microtubules that have a diameter of ~ 25 nm [94], and shows little tendency for aggregation [95].
27 Phosphorylation triggers tau-tau self-assembly [96]. Tau pseudophosphorylation on some sites found
28 preceding residue 208 mainly suppresses tau aggregation whereas tau pseudophosphorylation at sites
29 in the C-terminal region preferentially promotes tau self-association, particularly S422 [97, 98]. Tau
30 phosphorylation by GSK3 β induced tau aggregation [99, 100]. Two hexapeptides, ²⁷⁵VQJINK²⁸⁰ and
31 ³⁰⁶VQJVYK³¹¹, are effective in generating β -sheet structures while processing tau aggregation [101,
32 102].

33 Abnormal folding of the MAPT results into paired helical filaments (PHFs) and neurofibrillary
34 tangles (NFTs) [103]. The cores of PHFs and SFs are composed of eight β -sheets (β 1-8) that run along
35 the length of the protofilament, adopting a C-shaped architecture [104]. Hydrophobic clustering,
36 aliphatic stacking (V339, L344, V350, I354) and aromatic stacking (F346) stabilize the interior of β -helix
37 [104]. The existence of *in vitro* twisted ribbon-like assemblies of tau fibrils was observed, showing
38 corrugations with periodicities of 17.4 ± 2.7 nm ($n=16$) in fibrils of human tau40 [105].

39 In human AD cortex, soluble A β dimers induced tau hyperphosphorylation and neuritic
40 degeneration [106]. Therefore, A β is upstream of tau in AD pathogenesis and triggers the conversion
41 of tau from a normal to a toxic state, but there is also evidence that toxic tau enhances A β toxicity via
42 a feedback loop.

1 The above biochemical and biophysical properties of A β and tau nucleation and growth
2 provide key fundamental molecular insights which are the basis for effective mechanisms in delaying
3 neurodegenerative bioprocesses.

4 **4. General Structure of Polyphenols**

5 Among 8000 known polyphenolic compounds, more than 5000 flavonoids are widely
6 distributed in plants [107-109], e.g. tannins, in particular proanthocyanidins with more than 1000
7 derivatives identified to date. Tannins can be classified into two groups: hydrolysable tannins and
8 condensed tannins [110, 111]. The condensed tannins, also referred as proanthocyanidins, are the
9 most abundant. Hydrolysable gallotannins contain gallic acid (GA) substituents esterified with a polyol
10 residue (mainly D-glucose). The biosynthetic pathway, starting from D-glucose and after the
11 galloylation reaction, yields di-, tri-, tetra-, penta-, hexa-, hepta- and octagalloyl-glucoses. Gallotannin
12 with 10 (up to 12) units of GA esterified to a single glucose moiety are having many phenolic OHs, e.g.
13 tannic acid (TA) with 25 phenolic OHs. The majority of polyphenols have more than two aromatic rings,
14 essential for π - π stacking with aromatic amino acid residues of A β , and at least three phenolic hydroxyl
15 groups that can form hydrogen bonds with hydrophilic residues of A β [112].

16 **5. Mechanisms and Delaying Aggregation of A β and Tau**

17 There are various mechanisms for delaying A β and tau aggregation in the context of AD.
18 Natural polyphenols are known to strongly associate with these proteins, thus have the potential to
19 prevent protein self-association and the formation of toxic oligomers, fibrils and plaques. Different
20 aggregation mechanisms occur in human brain, such as: salt-induced aggregation, bulk aggregation,
21 and surface-induced aggregation (either on A β and tau fibrils from secondary nucleation, or on
22 biosurfaces other than A β - and tau-fibrils). Interestingly, polyphenols are stable in high conductivity
23 environments, such as physiological conditions.

24 Nucleated polymerization processes are involved in many growth phenomena in nature [113].
25 For example, the biology of human brain involves molecular and macromolecular growth bioprocesses.
26 This includes different A β and tau structures, conformations and shapes, such as aggregate, cluster,
27 dimer, fibril, fiber, monomer, neurofilament light (NfL), NFTs, oligomers paired helical filament (PHF),
28 plaque, protofibril, and straight filament (SF). Some of the above are structures within the colloidal
29 domain (~5 nm to 5 μ m) [80]. Smaller molecules with less than ten or fifteen amino acids (aa's) are
30 below this range, but protein oligomers of A β 40/42 and larger macromolecules such as tau protein
31 with more than about 100 aa's (e.g. tau441), are likely within this range. Nevertheless, the interactions
32 in both ranges are diffusion controlled (perikinetic).

33 Aggregate denotes dimers, trimers and higher order assemblies. The term oligomer often
34 refers to aggregates of 2-20mers [114]. Amyloid fibrils are linear aggregates with a repetitive cross-
35 beta structure. Primary nuclei can form during the lag phase from monomers in bulk solution. Then,
36 the proliferation of new aggregates takes place on fibrils catalytic surfaces, referred as secondary
37 nucleation [114, 115]. The lag phase can be minimized by addition of pre-formed nuclei or seeds [116].
38 Interestingly, a significant delay on the onset of A β 40 fibrils formation was reported at a low
39 apolipoprotein E3 (apoE3) concentration (40 nM), equivalent to an apoE3:A β molar ratio of 1:1000
40 [117].

41 **5.1 Salt-induced aggregation and Critical association concentration**

42 The formation of A β fibrils and other polypeptide aggregates strongly depends on the
43 physiological and chemical environment e.g., the type and salt concentration [118]. Jain et al. [119]

1 reported the impact of NaCl on the kinetics of A β fibril formation and β -rich oligomer formation, where
2 the aggregation rate significantly increased up to ~100 mM NaCl and reaches a plateau at about ~200
3 mM NaCl. Interestingly, the sodium concentration in human CSF and in serum was reported to be 145.3
4 to 147.7 mM [120]. Moreover, the aggregation kinetics and thermodynamics measurements yield the
5 following order of chloride cations for A β 40 peptide aggregation: Mg²⁺ > Li⁺ > Na⁺ > K⁺, while sodium
6 anions are ranked as: SO₄²⁻ > I⁻ > Cl⁻ > NO₃⁻ \approx ClO₄⁻ [118]. These series are known as lyotropic series and
7 are predicted from an extension of classical colloidal coagulation theory, by including the effects of
8 electroviscous drag [121, 122].

9 The critical association concentration of A β , or (CAC)_{A β} , represents the minimum concentration of A β
10 leading to self-association, which depends among other parameters on the salt concentrations. For
11 example, the experimental (CAC)_{A β 40} was reported to be: ~0.2 μ M [123], ~0.7-1 μ M [124], 0.88 +/- 0.07
12 μ M [125], and Hellstrand et al.[126] showed that spontaneous aggregation only occurs when A β 42
13 concentration is ~0.2 μ M, all in the presence of salt. Novo et al. [127] reported that the *in vitro* A β 42
14 critical aggregation concentration, under physiological conditions, is about 0.091 \pm 0.014 μ M.
15 However, since the experimental solubility of A β 42 is 0.04 μ M [78], (CAC)_{A β 42} in the absence of salt
16 should be less than 0.04 μ M.

17 5.2 Bulk-induced nucleation and growth

18 This type of mechanism suggests that A β and tau association and aggregation occur in bulk
19 solution, e.g. physiological fluid such as CSF and blood environment. In the case of A β 42 aggregation,
20 the key amyloid formation steps have been reported [128, 129] as: i) “the primary nucleation of new
21 aggregates from monomers in solution” [130-132], ii) “the addition of monomers to fibrils ends
22 resulting in their elongation” [76, 133, 134], and iii) “the secondary nucleation of monomers on the
23 fibrils surface” [128, 135, 136]. All the above three microscopic processes occur during all three
24 macroscopic phases (lag, growth and plateau), albeit at different rates, as governed by the rate
25 constants, and concentrations of reacting species at each point on time [114, 137, 138].

26 In bulk solution, the secondary nucleation process shows a much lower energy barrier than
27 primary nucleation (~10 times) [139], where the surfaces of existing amyloid fibrils is catalyzing the
28 formation of new pre-fibrillar aggregates from the soluble peptides [139, 140]. Moreover, Cohen et al.
29 [129] reported the free-energy landscape for secondary nucleation.

30 Strikingly, even though the oligomers are the key source of fibrils, less than 10% of A β 42
31 oligomers successfully converted into fibrillar species, whereas the remaining 90% of the oligomers
32 dissociated back to the monomeric form [141]. Michaels et al. [141], suggested that oligomer
33 dissociation is ‘spontaneous’, whereas oligomer upconversion involves additional interactions with
34 monomers, and may occur in bulk solution in contact with the fibril surface [142]. As for A β 42 and
35 A β 40, the vast majority of oligomers do not form fibrils, but rather dissociates back to monomers. This
36 type of mechanism, has been ascribed to a non-classical nucleation process for A β 42 amyloid fibrils
37 [141], but alternatively can be readily described by a dynamic equilibrium between oligomer formation
38 and break-up. Aggregates break up with a certain inherent rate constant and are formed by collisions,
39 which involve interactions between particles or molecules in solution. These processes are pH
40 dependent, as are other aggregation processes of proteins in general.

41 Frankel et al. [143] investigated the mechanisms underlying A β 42 aggregation (0.8–10 μ M) in
42 human CSF through the kinetic experiments, though in healthy humans A β 42 concentration in CSF is
43 around 250 pM. They also found that the aggregation process involves the same microscopic steps in
44 CSF as in pure buffer, but the secondary nucleation rate constant is decreased [143].

1 Natural polyphenolic molecules can alter and/or delay amyloid- β self-association and the
2 growth of oligomers/fibrils in bulk solution (Figure 2).

3 It is noteworthy that using AFM and mica sheets functionalized with 1-(3-aminopropyl)
4 silatrane (APS) showed that surface-induced aggregation occurs at a concentration at which no
5 aggregation in solution is observed [144], e.g. likely below the critical association concentration of A β .
6 The experiments were performed with full-size A β protein (A β 42, 0.1 μ M), a decapeptide A β (14-23)
7 (0.1 μ M) and α -synuclein (0.01 μ M); all three systems suggest a significant preference of the on-surface
8 aggregation pathway compared to the aggregation in the bulk solution [144].

9 5.3. Surface-induced aggregation on biosurfaces other than A β - and tau-fibrils

10 So far, we have reported A β elongation/aggregation on fibril surfaces which is consistent with
11 the related AD literature. However, other possible mechanisms must be highlighted since many more
12 biosurfaces in human brain are available for A β /tau adsorption and aggregation, thus probably
13 relevant to neurodegenerative diseases, such as AD.

14 In other words, aggregation can also occur on biosurfaces other than A β - and tau-fibrils, e.g.
15 membranes, vesicles, endosomes, exosomes, micelles, erythrocytes/red blood cells (RBC's), platelets,
16 albumin and blood vessels. The total length and surface area of human brain capillaries are \sim 600 km
17 and \sim 20 m², respectively [145, 146]. For example, A β can be cleared via perivascular drainage pathways
18 or deposited as neuritic plaques in the brain parenchyma or as cerebral amyloid angiopathy (CAA)
19 along vessel walls [147]. When A β deposition occurs in brain capillaries (CAA type I), it tends to be
20 widespread in the neocortex and hippocampus [148, 149], and associated with severe AD pathology
21 [149, 150].

22 The human tau (hTau40) is also highly surface active and preferentially interacts with
23 negatively charged membranes [151, 152]. Georgieva et al. [153] reported that lipid membranes
24 efficiently facilitate *in vitro* tau aggregation. For their part, Yu et al. [154] reported that human islet
25 amyloid polypeptide (hIAPP) aggregation was strongly enhanced by negatively charged membranes.

26 In addition, A β peptides interact with plasma proteins and RBC's surface [155-158]. In the
27 human body, 84% of the blood cells are RBCs and about 50% of the volume of blood (hematocrit)
28 consists of RBCs [159], having an overall negative charge [160]. In human blood, circulating blood cells
29 are exposed to nanomolar levels of soluble A β 40/42 [161]. Interestingly, A β deposits in
30 the extracellular space of the brain and on the walls of cerebral blood vessels, mainly capillaries. A
31 dynamic equilibrium between brain A β and plasma A β has been reported by DeMattos et al. [162]. Lan
32 et al. [157] showed that 98% of AD peripheral RBCs were amyloid binding-positive. Kiko et al. [163]
33 provided evidence that A β 40/42 were detected in RBCs. Moreover, A β 42 interacted with RBCs more
34 avidly than A β 40 [164]; *in vitro* and *in vivo* experiments suggested that A β induces oxidative damage
35 to RBCs [156, 164]. Morphological changes induced in RBCs, triggered by A β binding, was also observed
36 [157, 165]. Remarkably, A β and tau as well as alpha-syn/A β and alpha-syn/tau heterocomplexes were
37 also observed in RBCs [166, 167].

38 Interestingly, Koren et al. [168] postulated that circulating erythrocytes and likely also other
39 blood cells might be coated by polyphenols from nutrients. The binding of polyphenols [168] and
40 hydrolysable tannins [169] with RBC's surface membrane have also been observed. RBCs and
41 lipoproteins in blood showed to be reservoirs and transporters of polyphenols [170]. Harbi et al. [170]
42 also determined the concentration of polyphenols associated with RBCs (intracellular + surface-
43 bound); e.g. EGCG binds to RBCs' surface (33%) and intracellular (43%).

1 Moreover, A β peptides interact with platelet surfaces in a highly specific manner [171], with
2 platelet being 4.9% of the number of cells in human body [159], and the main source of A β peptides in
3 blood (~90%) [172, 173]. Wolozin et al. [171] also found that low levels of soluble A β (0.1-1 nM)
4 augment adenosine-diphosphate(ADP)-dependent platelet aggregation. However, the ingestion of the
5 polyphenol quercetin-4'-O- β -D-glucoside inhibited platelet aggregation in humans [174].
6 Nevertheless, the impact of polyphenols on aggregation might differ whether platelets are activated
7 or not [175].

8 Biere et al.[176] found that the large majority of A β (~89%) is bound to albumin and specific
9 lipoproteins in human plasma. Albumin is also an A β carrier [177]. Interestingly, Yeggoni et al.[178]
10 showed that the natural polyphenol corilagin binds to human serum albumin (HSA) and found the
11 experimental binding constant of the complex to be $4.2 \pm 0.02 \times 10^5$ /mol with a free energy of -7.6
12 kcal/mol, also supported by their computational MD results.

13 Real-time precise determination of the growth rates of protein aggregates on surfaces can be
14 measured using a quartz crystal oscillator (surface) [179]. Although the quartz crystal microbalance
15 with dissipation (QCMD) method [180] proved to be reliable to study A β aggregation [181, 182], there
16 are very few publications on the interactions between polyphenols and A β on surfaces. For example,
17 Wang et al. [183] showed a reduction of ~65% of the growth rates of A β monomer on curcumin-
18 induced aggregates. By using QCMD combined with liquid AFM, Yu et al. [154] observations pointed
19 toward a surface-involved pathway of protein adsorption and 2D amyloid aggregation. Surface
20 plasmon resonance (SPR) also showed to be an effective method to study the kinetic of A β 42
21 aggregation on carboxylated dextran-modified surfaces [184].

22 5.3.1 Surface-induced aggregation

23 Considering that A β [144] and tau [151-153] proteins are highly surface active and
24 preferentially interact with negatively charged membranes, this can trigger adsorption on membranes
25 followed by surface-induced aggregation where protein can interact with other proteins and
26 polyphenols. Importantly, human physiological A β [143, 185, 186] and tau [187] concentrations are in
27 the low nanomolar range. In 2017, Barnejee et al. [144] reported that on-surface *in vitro* aggregation
28 of A β and α -synuclein occurs at a concentration at which no aggregation in bulk solution is observed.
29 Interestingly, in 2005 we proposed that surface-induced aggregation/clustering occurs, causing an
30 induction period [188, 189].

31 Consequently, a strategy where surface-induced aggregation occurring below the critical
32 aggregation concentration of A β and tau, treated at the earliest stage, might result in minimizing
33 protein self-association, slowing down the aggregation processes and delaying the progression of AD.

34 5.3.2 Proposed concept: confinement stability

35 The adsorption of A β and tau on biosurfaces other than A β - and tau-fibrils, e.g. membranes,
36 vessels, albumin, red blood cells (RBCs), etc., can lead to confinement stabilization, a new concept
37 recently proposed [190]. For example, figure 3 shows that: A β and/or tau proteins (left) and phenolic
38 ligands (center), are confined and stabilized on RBC's biosurfaces (red), which then prevents protein
39 self-association and slows down the aggregation process, hence delaying the progression of AD.
40 Moreover, polyphenolic ligands can associate with A β and/or tau proteins, forming complexes (right),
41 and thus prevent or inhibit self-association and aggregation of these proteins.

42 The adsorption and confinement of soluble A β and tau on biosurfaces potentially influences a
43 number of phenomena that might occur, such as structural changes, reconfiguration, increased local

1 protein concentration, decreased protein entropy, alteration of physiological functions, and formation
2 of toxic A β -oligomers and/or protofibrils, tau NFTs, etc. Moreover, these confined and stabilized
3 proteins are unable to diffuse and collide with other proteins and/or cells in bulk solutions.
4 Confinement also occurs in hydrogels and tissues where it modifies the folding and aggregation of
5 proteins [191-193].

6 In AD, the impact of small molecules (proteins, polyphenols) and nanoparticles that are
7 stabilized by RBCs/platelets/vessel walls/etc., through confinement stability, is still to be enlightened.
8 Although RBC perturbation by A β protein has been reported [156], our hypothesis is that the overall
9 impact of polyphenols will be beneficial since they will bind to A β and/or tau proteins, e.g. resulting in
10 less oxidative damage.

11 We expect that our proposed concept of “confinement stability” highlights new and additional
12 mechanisms implicating A β and tau pathways in the physiopathology of NDs, such as AD.
13 Consequently, research is necessary not only to elucidate direct but also indirect pathways
14 involving surface-induced processes occurring on biosurfaces other than A β - and tau-fibrils.

15 **6. Therapeutic Strategies for Decreasing A β and Tau Production and** 16 **Aggregation**

17 The complexity of A β /tau production and aggregation pathways, the role of the
18 monomer/oligomers or aggregated forms of A β /tau, and the unknowns regarding the progression of
19 AD highlight the challenges for the discovery of effective treatments to delay or prevent this disease.
20 For the amyloidopathy, some strategies targeting the amyloidogenic pathways (e.g. β -secretase (BACE)
21 inhibitor [194-197], the non-amyloidogenic pathways (e.g. α -secretase activator), as well as the γ -
22 secretase inhibitors and modulators (GSM) (e.g. [198]) were developed with limited success. For the
23 tauopathy, some of the most promising therapies have been discussed by Simic et al. [199]: minimize
24 tau phosphorylation, proteolysis, aggregation, clearance of intra- and extra-cellular tau, and
25 microtubules stabilization. Nevertheless, the need for fundamental understanding of A β and tau
26 kinetics as well as aggregation inhibitors is imperative.

27 One strategy to mitigate AD may be the development of neuroprotective agents to prevent
28 protein self-association, reduce A β and tau aggregation and/or induce the formation of non-toxic A β
29 oligomers/tau NFTs. For example, polyphenolic ligand might prevent or delay A β and/or tau self-
30 association at the earliest stage, e.g. below the critical association concentration of A β and tau
31 proteins.

32 Table 1 shows molecular and pharmacological properties of some natural polyphenols and one
33 commercial synthetic drug for comparison, e.g. donepezil (Aricept) an acetylcholinesterase inhibitor
34 [200-203]. As expected, polyphenols are far less toxic than donepezil. For example, corilagin (β -1-O-
35 Galloyl-3,6-(R)-hexahydroxydiphenoyl-D-Glucose) [204, 205] has an LD50 between 3500-5000 mg/kg
36 b.wt. [206], suggesting a very low toxicity even at high dosages [206, 207] (Table 1). Moreover,
37 corilagin, a hydrolysable tannin, shows numerous pharmacological properties [208-213]. Corilagin
38 (more rigid) is a close analogue of 1,3,6-tri-O-galloyl- β -D-glucose (TGG) (more flexible), with similar
39 molecular properties (Table 1) [84, 204]. This type of molecules also has remarkable properties for
40 stabilizing and/or destabilizing colloidal systems [188, 189]. For example, we proposed a surface-
41 induced clustering mechanism where corilagin/poly(ethylene oxide) clusters slowly built on micro-
42 cellulose surfaces (corresponding to the induction period) [189]. Very little or no research has been
43 performed on the inhibiting effects of corilagin and TGG on the kinetics of A β and tau
44 aggregation/disaggregation bioprocesses. Nonetheless, their complementary structures (rigid vs

flexible) might be relevant in the context of AD [84]. For comparison, 1,2,3,4,6-penta-O-galloyl- β -D-glucopyranose (PGG) alone inhibited: i) A β 40/A β 42 fibril formation; ii) A β aggregation at low concentrations (IC₅₀ = 3 μ M); and iii) neurotoxic A β oligomer formation [214]. Interestingly, both TGG and PGG molecules share similar properties, e.g. hydrophobicity and flexibility [84, 204]. Consequently, both natural polyphenols corilagin and TGG have these physicochemical attributes, thus potential candidates for AD treatment.

In addition, the effective concentrations (EC₅₀) of TA on the formation, extension, and destabilization of preformed amyloid- β fibrils (fA β 40 and fA β 42), are in the order of less than 0.1 μ M [215], and the *in vitro* IC₅₀ are 0.012 and 0.022 μ M for A β 40 and A β 42, respectively [216]. TA also inhibited the *in vitro* aggregation of tau peptide R3, with an IC₅₀ of 3.5 μ M [217]; however, the inhibitor GA was less effective with an IC₅₀ of 92 μ M [217]. Moreover, TA shows low toxicity, e.g. LD₅₀ of 2260 mg/kg (oral rat) (Table 1).

EGCG, with an LD₅₀ of 2170 mg/kg (mice), remodels large oligomers/fibrils into less toxic off-pathway assemblies [218]. Among fifteen secondary metabolites from plants, EGCG, myricetin, silibinin, and luteolin lowered the A β aggregation below 40% [219]. Moreover, EGCG inhibited the *in vitro* tau aggregation [220], in addition both EGCG and curcumin facilitated clearance of hyperphosphorylated tau [218].

There is a wide variety of mechanisms by which polyphenols show neuroprotective effects [221]. For instance, earlier studies have reported IC₅₀ values of myricetin against of A β 40 and A β 42 aggregation within 0.2 to 0.9 μ M [222, 223]. Moreover, fisetin (3,3',4',7-tetrahydroxyflavone) inhibited A β 42 aggregation [224]. Their results suggest that the 3',4'-dihydroxyl group, but not the 3- or 7-hydroxyl group, is critical for the inhibitory effect on the formation of A β 42 fibrils [224]. The polyphenol isomers vescalagin and castalagin protect SH-SY5Y neuroblastoma cells by reducing the toxicity of A β 42-oligomers [225]. Vescalagin totally inhibited aggregation at an A β 42:polyphenol ratio of 1:1. Both vescalagin and castalagin decreased the amount of parallel β -sheets, and induced rearrangement of peptides into helix, anti-parallel β -sheets and other secondary structures [225]. Morin attenuates tau hyperphosphorylation by inhibiting GSK3 β , implicated in AD pathogenesis, and showed the strongest inhibition in the GSK3 β activity assay [226].

Potential strategies for effective anti-dementia drugs do not only focus on the inhibition of oligomer/fibril formation, but also the destabilization/disaggregation of pre-aggregated A β - and/or tau-fibrils, or a combination of them. Unsurprisingly, numerous polyphenols have this ability as evidenced in the following section.

7. Destabilization and Disaggregation of A β and Tau

Fibrils destabilization serves the dual purpose of deformed fibrils becoming non-neurotoxic themselves and further inhibiting the formation of higher-order aggregates [227, 228]. Freysson et al. [229] reported the significant role of polyphenols on aggregation and disaggregation of amyloid peptides, tau and α -synuclein, in line with dispersive properties of polyphenols such as tannins [230].

Bieschke et al. [231] showed EGCG to inhibit A β 42 fibrillogenesis, but also the ability to convert large, mature A β fibrils into smaller amorphous protein aggregates. Immuno-infrared sensor data are consistent with the degradation of A β fibrils induced by EGCG [232]. Gallic acid was shown to inhibit amyloid fibril formation (molar ratio A β :GA of 1:2) and to disaggregate preformed fibrils [233, 234]. Adding GA to the aggregated A β 42 fibrils for 2 hours clearly reduced the A β 42 fibril particle size from predominantly 100 nm fibrils to ~60 nm [234]. Fujiwara et al. [214] showed, *in vitro* and *in vivo*, that PGG disaggregated preformed A β fibrils. After incubation of 25 μ M of fresh fA β 40 and fA β 42 with 50

1 μM TA, Ono et al. [215] showed that TA destabilized preformed A β fibrils. Liu et al. [233] proposed that
2 the gallate group in GA (and related compounds) is the structural motif that prevents fibril formation.

3 Curcumin showed *in vivo* [235], and *in vitro* [227], the ability to inhibit A β aggregation and to
4 disaggregate preformed A β fibrils. The activity on insulin-degrading enzyme (IDE) toward A β 42 in the
5 presence of resveratrol results in a substantial increase in A β 42 fragmentation compared to the control
6 [236]. Sun et al. [237] demonstrated that tau alone gave long fibrils, while 50 μM resveratrol (RSV)
7 induced the formation of short tau fibrils, and 200 μM RSV led to smaller aggregates. Vion et al. [238]
8 showed that both resveratrol and trans ϵ -viniferin, at 1 μM , induced disaggregation of pre-aggregated
9 A β 42 peptide. Caillaud et al. [239] also reported that trans ϵ -viniferin reduces the size and density of
10 amyloid deposits and decreases reactivity of astrocytes and microglia.

11 Khan et al. [240] provided a synopsis on the relationship between quercetin and cognitive
12 performance in AD. Quercetin and rutin inhibit the formation of A β fibrils and disaggregated A β -fibrils
13 [195]. Moreover, quercetin displays fibril destabilizing effects on preformed fibrillar A β , reversing A β -
14 induced neurotoxicity [241]. Dihydroquercetin (Taxifolin), also disassemble A β *in vitro*, reduced levels
15 of A β oligomers *in vivo*, and restored decreased cerebral blood flow as well as cerebrovascular
16 reactivity in Tg-SwDI mice [61].

17 Dihydromyricetin or anthocyanins/anthocyanins also reduces fibrils formation and
18 disaggregates preformed fibrils [242-244]. Interestingly, only amorphous aggregates were formed
19 when the molar ratio of A β 40 to dihydromyricetin was 1:3 [243].

20 Although Alzheimer's pathways and the related polyphenols are constantly investigated, the
21 Gordian knot has not been untied yet. To solve this problem, we still need additional scientific
22 knowledge and tools. For example, many questions related to NDs cannot be handled experimentally
23 and could benefit by using advanced computational molecular methods.

24 **8. Computer Simulation of Phenolic Ligands with A β and Tau**

25 After decades of experimental research where major advancements have been achieved, we
26 still need to identify the real cause of AD. Consequently, computational methods, often named '*in*
27 *silico*' approaches, can accelerate the development, where scientists can generate experimental data
28 while molecular theoretical calculations are processing. However, even after almost 20 years of
29 amyloid aggregation MD simulations there are still limitations, more specifically: force field, protein
30 concentration and simulation length challenges [245].

31 Molecular modeling (MM) encompasses all theoretical and computational methods used to
32 model or mimic molecular behavior. MM development began in the early 1960s, although the
33 underlying math originated much earlier. The common feature of all MM methods is the atomistic-
34 level insights it provides. Numerous methods exist: e.g., molecular mechanics [246], semi-empirical
35 [247, 248], density functional theory (DFT) [249], molecular dynamics (MD) [250], ab-initio [251], as
36 well as sampling methods such as replica exchange molecular dynamics (REMD) [252-254], and
37 molecular docking [255-257]. The selection of methods hinges on whether a quick answer from
38 classical methods (e.g. molecular mechanics) is desired, as opposed to highly accurate results from
39 quantum mechanics-based calculations (e.g., ab-initio molecular orbital calculations) but time-
40 consuming.

41 The therapeutic area where computational methods impact most is in the small-molecule drug
42 discovery area, e.g. polyphenols. Virtually all small molecule drugs work by binding to proteins,
43 enzymes, receptors, and ion channels, and sometimes DNA or RNA. The binding of small molecule, or

1 ligand, to the targeted protein induces a biological response. Small molecule drugs are popular,
2 because they are easy to produce, distribute and administer, and easily chemically modified to fine
3 tune the effects of the drug. Modelling methods can guide chemists to synthesize molecules with
4 improved binding to the protein, its activity. By improving the binding of the target molecule with the
5 desired protein target and reducing binding with undesirable related protein targets, ligands can be
6 made more selective, an attribute which reduces many side effects. Generally, pharmacokinetic
7 properties can be predicted with an in-silico method, allowing researchers to avoid wasting resources
8 on compounds that will either be too toxic, or have the wrong biological transport properties for a
9 successful drug. In silico methods are a way of reducing the chemical search space, by helping to design
10 experiments, and glean as much information as possible, from existing experimental data.

11 Given the experimental difficulties in terms of predictability from mouse to human in *vitro*/*in*
12 *vivo* clinical experiments, computer modelling (in silico) has emerged as a reliable tool to elucidate
13 brain chemistry. Due to their importance and size, both highly intrinsic disordered A β 40 and A β 42
14 proteins have been extensively studied. For example, using a coarse-grained force field coupled to
15 Hamiltonian-temperature replica exchange MD simulations, the equilibrium structures of A β 40, A β 42,
16 and A β 40 (D23N) monomers [258], and dimers [259], were determined. They observed striking
17 morphological differences [258], and they also showed that A β 42 dimer has a higher propensity than
18 A β 40 dimer to form β -strands at the central hydrophobic core (residues 17-21) and C-terminal
19 (residues 30-42), i.e. critical segments for A β oligomerization. Chiricotto et al. [260] applied the multi-
20 scale Lattice Boltzmann Molecular Dynamics method (LBMD) to study the initial phases of the
21 hydrophobic central core of amyloid peptide (A β 16–22; KLVFFAE) aggregation.

22 Using MD simulations, Zhao et al. [261] studied the early adsorption and conformational
23 change of A β oligomers from dimer to hexamer on three different self-assembled monolayers (SAMs)
24 terminated with CH₃, OH, and COOH groups. Combining with experimental results, all SAM model
25 surfaces exhibited a seeding effect for A β polymerization [261].

26 Results from the virtual oligomerization inhibition (VOI) were in excellent agreement with the
27 experimental results, of the performance of six known A β aggregation inhibitors: brazilin, curcumin,
28 EGCG, ELND005, resveratrol, and tacrine [262]. However, only EGCG is still active at phase III, while
29 some of them were terminated due to the lack of efficacy. The EGCG ligand strongly interacted with
30 most residues of A β 16–22, notably F19 and F20. Interestingly, with EGCG the oligomerization time was
31 significantly delayed: e.g., i) control (7, 20 and 48 ns), and EGCG-A β 16–22 (16, 50, and 106 ns), for
32 dimer, trimer and tetramer, respectively [262]. Using a combination of *in vitro* experimental
33 measurements and in silico methods, Acharya et al. [232] found that the most favorable GlideScore
34 (–6.9; docking site #1) was obtained when EGCG binds inside the fibril, stabilized by π -stacking
35 interactions with residue F19 [232]. Zhan et al. [263] showed both EGCG and EGC disruptive capacity
36 on the newly cryo-EM resolved LS-shaped A β 42 protofibrils by breaking the hydrogen bond between
37 H6 and E11 through π – π interactions with residues H14/Y10 and hydrogen-bonding interactions with
38 E11 [263].

39 The interactions between dihydromyricetin and A β 40 trimer were mainly nonpolar, and where
40 MD simulation showed the key A β 40 interacting residues are V18, A21, D23 [243]. Mechanistic insights
41 from MD suggest that morin can penetrate into the A β 42 hydrophobic core to disrupt the Asp23-Lys28
42 salt bridge and interfere with backbone hydrogen bonding [264]. Also, Lemkul et al. [264] reported
43 that morin inhibits the early stages of A β -peptide aggregation. Gargari and Barzegar [265] showed that
44 flavonoids (myricetin, morin) exert dual and more effective functions against monomeric aggregation-
45 prone state (fibrillogenesis suppression) and remodel the A β aggregation pathway (fibril
46 destabilization).

1 Cyanidin-3-O-glucoside (Cy-3-G) inhibits A β 40 fibrillogenesis, disrupts the β -sheet structure,
2 disaggregates preformed fibrils, and reduces amyloid cytotoxicity [266], e.g., when the A β 40: Cy-3G
3 ratio was 1:3, the inhibitory effect on A β 40 fibril formation was about 95%. Cy-3G mainly interacted
4 with: N-terminal region, central hydrophobic cluster and β -sheet region II via hydrophobic and
5 electrostatic interactions [266].

6 In *vitro* and in *silico* results from Gu eroux et al. [267], showed the ability of some polyphenols
7 from the procyanidin family, to specifically bind the proline-rich region of tau. Interestingly, the
8 galloylated procyanidins ECG and EGCG exhibit a higher affinity with respect to the non-galloylated
9 procyanidins [267]. Theoretical and experimental results indicated that tau interacts with TA by
10 forming a hairpin structure, hence, a feature for inhibiting tau polymerization [217].

11 More than ever, computing capacity and MM methods are transforming our understanding of
12 the brain chemistry and more specifically the underlying mechanisms of amyloid peptides aggregation
13 and disaggregation involved in NDs, such as AD.

14 **9. Conclusions**

15 Physicochemical interactions between protein and natural ligands play a major role in
16 numerous bioprocesses. Those have to be addressed to better understand the mechanisms and
17 responses of natural polyphenolic ligands/protein complexation. The A β peptide is an endogenous
18 compound involved in several NDs, such as AD which nucleates decades before a conclusive diagnostic.
19 The amyloid-cascade hypothesis has provided the main framework for understanding the AD
20 pathogenesis, where the basis is the pathogenic A β peptides aggregation into neuritic plaques. Yet,
21 this hypothesis must integrate the contributions of other proteins such as tau, which is involved in
22 more than 20 neurodegenerative diseases, including AD. Consequently, it is critical to intervene at the
23 earliest stage (e.g. nucleation, induction period) of the disease and to select the effective chemistry
24 with the right mechanisms. This complex task, not only needs highly sophisticated medical
25 experimental knowledge, but also theoretical molecular methods which helps to explore the
26 underlying mechanisms. To achieve this, a multidisciplinary approach, combining experimental and
27 theoretical methods, can be more effective to characterize the biochemical and biophysical
28 interactions between proteins and phenolic ligands.

29 Many pathways have been investigated to mitigate and delay amyloid- and tau-opathies, e.g.:
30 targeting amyloidogenic pathways (e.g. β -secretase (BACE) inhibitor), and non-amyloidogenic
31 pathways (e.g. α -secretase activator) as well as γ -secretase inhibitors and modulators (GSM), inhibit
32 the nucleation process of formation of oligomers/protofibrils/fibrils, alter/reduce oligomer/NFTs
33 cytotoxicity, disaggregate pre-aggregated fibrils, etc. Nonetheless, one critical pathway is to prevent
34 self-association at the early stages of AD (induction period), and below the A β and tau critical
35 association concentrations.

36 The pathways described in this review are mainly related to amyloid- and tau-based surfaces
37 (e.g. protofibrils, fibrils, fibers, NFTs, etc). However, our review suggests a sub-ensemble which
38 includes surface-induced processes occurring on biosurfaces other than A β - and tau-fibrils, e.g.
39 membranes, vesicles, blood vessels, red blood cells (RBCs), platelets, and likely relevant to NDs. For
40 example, the adsorption of A β and tau on RBCs biosurfaces, can either lead to confinement
41 stabilization or to surface-induced aggregation, depending on the affinity of A β and tau, and
42 A β /phenolic ligand complexes, to these surfaces. Bioprocesses occurring on surfaces other than A β -
43 and tau-fibrils, can be analyzed under a new concept, referred as confinement stability (figure 2). For
44 example, adsorption of A β /tau proteins, phenolic ligands and A β /phenolic ligand complexes on human

1 RBC's biosurface, results in stability by confinement, i.e. these proteins, ligands and complexes are
2 unable to aggregate due to temporary or permanent confinement. Overall, this sub-ensemble may
3 also participate indirectly in mitigating neurodegenerative diseases, by preventing protein self-
4 association, slowing down the aggregation process, and delaying the progression of AD.

5 In any case, it is imperative to develop strategic pathways that will work at the very early stages and
6 below the critical association concentration (CAC) of A β and tau, i.e. even before they form dimers,
7 trimers and oligomers.

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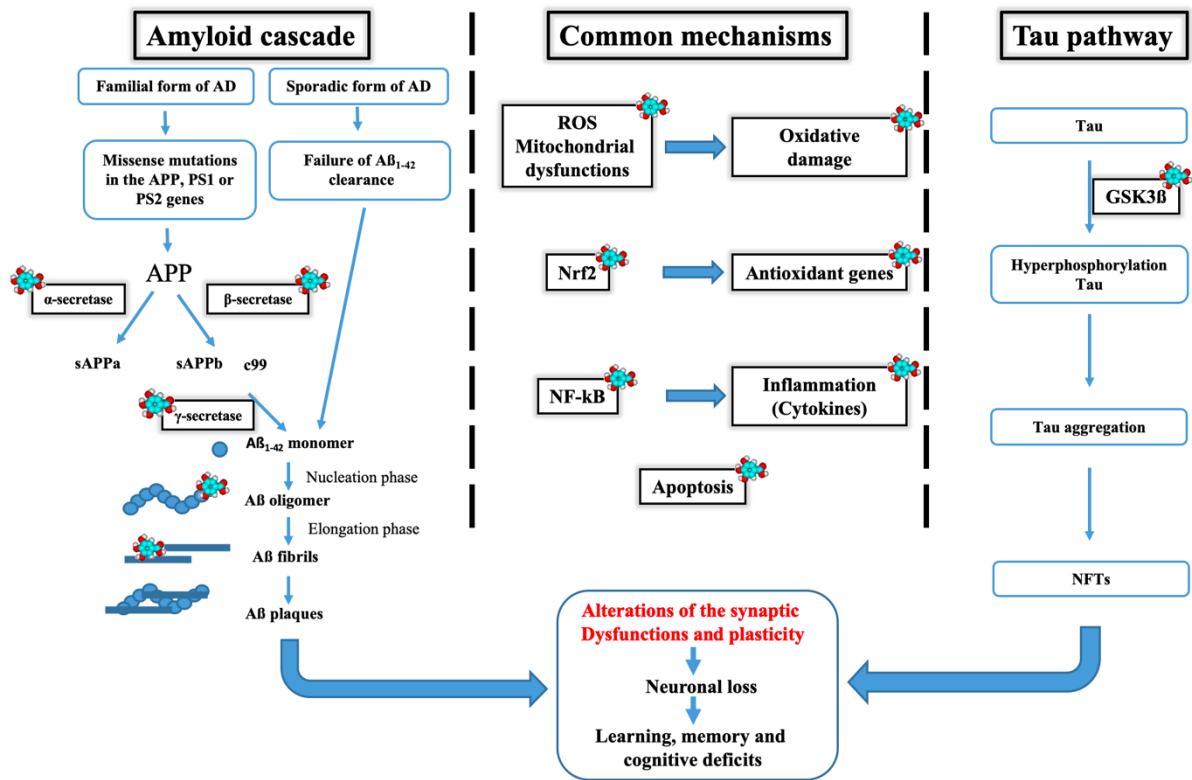
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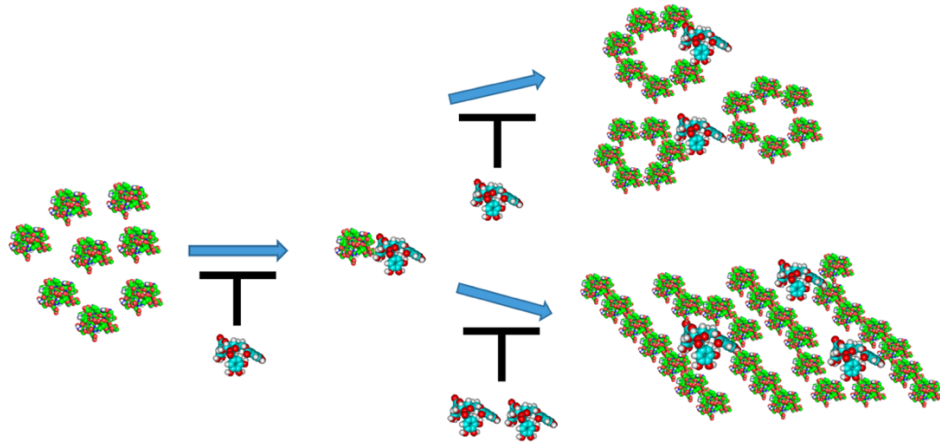
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Figure 1: Multiple targets of polyphenols in the integrative amyloid-cascade and tau pathway. Both $A\beta$ and tau pathology are independent and dependent pathways leading to AD. In familial form of AD, different mutations on APP, PS1 and PS2 genes lead $A\beta_{1-42}$ overproduction while in sporadic form of AD, failure of the $A\beta_{1-42}$ clearance under physiological conditions induced its gradual rising. The net result is to enhance the production of the putatively neurotoxic $A\beta_{1-42}$ monomer at the expense of the putatively neuroprotective $A\beta_{40}$. $A\beta_{1-42}$ accumulation into soluble oligomers induce oxidative damage, inhibit the activity of Nrf2 and thus the antioxidant genes, activate NF- κ B and the production of cytokines and finally cause apoptosis. $A\beta_{1-42}$, ROS, oxidative damage can activate glycogen synthase kinase 3 β (GSK3 β) which phosphorylate Tau protein. Both the formation of NFTs due to the hyperphosphorylation of Tau and the amyloid cascade lead to synaptic dysfunction, neuronal loss and finally to learning and cognitive impairment. () Represent different pathways targeted by polyphenolic compounds.

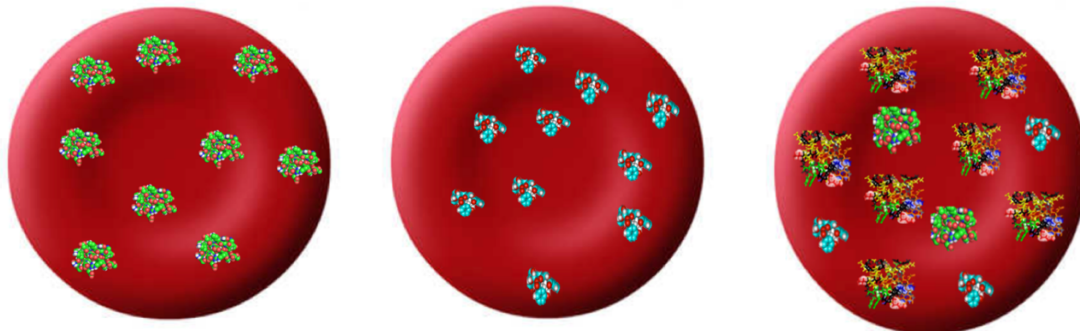


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2 **Figure 2:** Hypothesis of phenolic-induced altering and/or delaying amyloid- β ($A\beta$) self-association and the growth
 3 of oligomers/fibrils in bulk solution: (left) monomers of $A\beta$; (middle) $A\beta$ /phenolic ligand complex; (right-top) $A\beta$ -
 4 oligomers and complexed with phenolic ligands; and (right-bottom) $A\beta$ -fibrils and complexed with phenolic
 5 ligands. The $A\beta$ protein is green/red colored and the phenolic ligand is blue/red colored. The black T-shape
 6 symbol refers to inhibition/delaying the growth of oligomers/fibrils. This cartoon is not to scale; i.e. the phenolic
 7 ligand is much smaller than $A\beta$ -protein.

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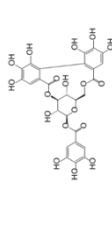
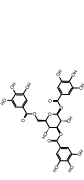
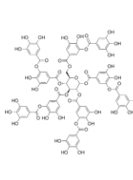
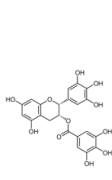
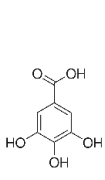
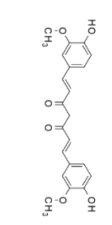
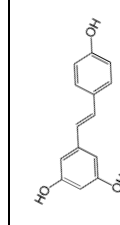
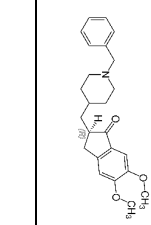
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10 **Figure 3:** A schematic of confinement stability: Adsorption of $A\beta$ proteins (left), phenolic ligands (center) and
 11 $A\beta$ /phenolic ligand complexes (right) on human RBC's biosurface (red), results in stability by confinement, i.e.
 12 these proteins and ligands are unable to aggregate due to temporary or permanent confinement. This cartoon is
 13 not to scale, i.e. $A\beta$, ligand and complexes are much smaller than indicated (RBC's diameter ~ 7.5 - $8.7 \mu\text{m}$ [268]).

14

1 **Table 1:** Molecular and pharmacological properties of some natural polyphenols related to A β and Tau
 2 aggregation/disaggregation and comparison with donepezil.

Parameters	Corilagin	TGG	Tannic Acid (TA)	EGCG	Gallic Acid (GA)	Curcumin (Keto)	Resveratrol (RES)	Donepezil; Aricept
Molecular structure								
Type of molecule	Tannin	Tannin	Tannin	Flavonoid	Phenolic acid	Curcuminoid	Stilbenoid	Synthetic
Molecular Formula	C ₂₇ H ₂₂ O ₁₈	C ₂₇ H ₂₄ O ₁₈	C ₇₆ H ₅₂ O ₄₆	C ₂₂ H ₁₈ O ₁₁	C ₇ H ₆ O ₅	C ₂₁ H ₂₀ O ₆	C ₁₄ H ₁₂ O ₃	C ₂₄ H ₂₉ NO ₃
Molar mass (g/mol)	634	636	1701	458	170	368	228	379
Inhibition of A β /Tau aggregation	Yes ^a /Yes	Yes ^a /Yes	Yes/Yes	Yes/Yes	Yes/?	Yes/Yes	Yes/Yes	Yes/Yes
Disaggregation of A β -/Tau-fibrils	NA/NA	NA/NA	Yes/?	Yes/?	Yes/?	Yes/?	Yes/Yes	?/?
Enzymes inhibition or enhancement	BACE1 ^b (IC50=34 μ M); PEP ^c (IC50=0.236 μ M)	PEP ^c (IC50 = 0.157 μ M)	BACE	Enhances α -Secretase ^d	?	BACE	Promotes non-amyloidogenic pathways ^e	AChE, BACE1
Hydrolysable	Yes	Yes	Yes	Yes	?	Yes	Yes	No
Phenolic rings (#)	Yes (3)	Yes (3)	Yes (10)	Yes (3)	Yes (1)	Yes (2)	Yes (2)	No (0)
Phenolic-OH (#)	9	9	25	8	3	2	3	0
Hydrophobicity	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Solubility in water (g/L)	5.0 in PBS @pH 7.2	1.6 @pH 5-7	Very high	~5	11.9 @20°C	0.4 @pH 7.3	~0.03	0.00293 @25°C
Biotransformation (metabolites/derivatives)	EA, GA, M3 ^f	GA	GA, PY	GA, EGC, EGC-M5,	4-OMGA	DHC, THC	Trans-RES-3-O-glucuronide ^g	?
Bioavailability (Oral)	?	NA	NA	Low (~0.1-0.26%)	High	Low	Poor (< 1%)	Very high
Toxicity LD ₅₀ (mg/kg per b.weight)	3500-5000 (mice)	NA	2260 (Oral rat)	2170 (mice)	5000 (Oral rat)	>2000 (mice)	7060 (rat)	32.6 (Oral rat)

3 Corilagin (β -1-O-Galloyl-3,6-(R)-hexahydroxydiphenoyl-D-Glucose); TGG (1,3,6-Tri-O-Galloyl- β -D-Glucose); EGCG
 4 (Epigallocatechin-3-gallate); ^aBinding with A β based on theoretical calculations (MD and HREX); MD= Molecular dynamics;
 5 HREX= Hamiltonian Replica Exchange; ^b[269]; ^cPEP = Propyl endopeptidase enzyme [270]; ^d[218]; ^eDecreases the level of A β
 6 by inducing non-amyloidogenic cleavage of APP [271, 272]; ^fCorilagin hydrolyzed metabolites (EA, GA and M3 (C₂₀H₁₈O₁₄)
 7 [273, 274]); ^gPrimary metabolite in human liver (Trans-RES-3-O-glucuronide) [274, 275]; NA= Not available; EA= Ellagic acid;
 8 EGC= Epigallo-catechin; PY= Pyrogallol; EGC-M5=5-(3', 4', 5'-trihydroxyphenyl)- γ -valerolactone and 5-(3', 4'-
 9 dihydroxyphenyl)- γ -valerolactone (human major urinary metabolites of tea polyphenols); PBS= Phosphate-buffered saline;
 10 DHC= dehydrocurcumin; THC= tetrahydrocurcumin; 4-OMGA= 4-O-methylgallic acid.