

Mitigating Alzheimer's Disease with Natural Polyphenols: A Review



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Abstract: According to Alzheimer's Disease International (ADI), nearly 50 million people worldwide were living with dementia in 2017, and this number is expected to triple by 2050. Despite years of research in this field, the root cause and mechanisms responsible for Alzheimer's disease (AD) have not been fully elucidated yet. Moreover, promising preclinical results have repeatedly failed to translate into patient treatments. Until now, none of the molecules targeting AD has successfully passed the Phase III trial. Although natural molecules have been extensively studied, they normally require high concentrations to be effective; alternately, they are too large to cross the blood-brain barrier (BBB).

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In this review, we report AD treatment strategies, with a virtually exclusive focus on green chemistry (natural phenolic molecules). These include therapeutic strategies for decreasing amyloid- β (A β) production, preventing and/or altering A β aggregation, and reducing oligomers cytotoxicity such as curcumin, (-)-epigallocatechin-3-gallate (EGCG), morin, resveratrol, tannic acid, and other natural green molecules. We also examine whether consideration should be given to potential candidates used outside of medicine and nutrition, through a discussion of two intermediate-sized green molecules, with very similar molecular structures and key properties, which exhibit potential in mitigating Alzheimer's disease.

Keywords: Alzheimer's disease, beta-amyloid, polyphenols, green chemistry, corilagin, 1,3,6-tri-O-galloy- β -D-glucose (TGG).

1. INTRODUCTION

Alzheimer's disease ((AD) OMIM 104300) is the most common age-related neurodegenerative disorder. Its clinical symptoms result from the deterioration of selective cognitive domains, particularly those related to memory [1]. According to Alzheimer's Disease International (ADI), nearly 50 million individuals worldwide were living with dementia in 2017, and this number is projected to triple by 2050 [2]. Livingston *et al.* [2] have calculated that over a third of all cases of dementia (derived from the Latin words *de* (out of) and *mens* (mind)) might be preventable. Interestingly, in the past two decades, the incidence rates of dementia have fallen by up to 20% in high-income countries such as the United States, the United Kingdom, and Canada [2, 3]. This trend cannot be ascribed to better treatment, as no effective therapies for halting Alzheimer's disease currently exist [4]. This effect is likely due to lifestyle changes in citizens of high-income countries [4].

Although the disease was first described in 1907 by Alois Alzheimer [5], the discovery that the extracellular plaques consist of aggregates of a small peptide called amyloid- β (A β), [6, 7] was not made until the mid-1980s. Not long thereafter, the existence of intracellular A β was first noted

in the literature [1]. In the late 1980s, it was discovered that neurofibrillary tangles (NFT) are aggregates of the tau protein [8].

The consequences of these pathological changes, including the effects of the A β and tau pathologies, include severe neuronal and synaptic dysfunction and loss; at death, the brain of an AD patient may weigh one-third less than that of an age-matched, non-demented individual [1]. The prevalence and incidence of AD suggest that age is the most influential known risk factor [9], with the exception of familial mutations leading to Early-Onset Amyloid Disease (EOAD) [10]. For those above age 65, the risk of developing Alzheimer's disease doubles every five years [4]. The two main pathological hallmarks of AD are extracellular amyloid-beta plaques (A β), a 4-kDa peptide (39 to 43 amino acids) derived from a much larger protein, the 80-kDa β -Amyloid Precursor Protein (APP) [11], and intracellular structures composed predominantly of a hyperphosphorylated, aggregated form of the microtubule-binding protein, tau [8, 12-17]. In AD, tau becomes hyperphosphorylated; this form of tau dissociates from microtubules and tends to self-aggregate, forming NFTs in cell bodies and dystrophic neurites [18]. Impairment of multiple cellular functions by A β and tau has been demonstrated in cellular and transgenic models, and crosstalk between these molecules has been demonstrated, particularly at the synapse [19]. Although A β may be secreted both pre- and postsynaptically [20], most axonally-secreted fragments are endocytosed in the soma,

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processed, and then transported to the pre-synapse [21]. Amyloid deposition appears to begin over a decade prior to the onset of cognitive deficit and a clinical diagnosis of AD [18, 22, 23]. According to the Amyloid Cascade Hypothesis, the primary influence driving AD pathogenesis is accumulation of A β in the brain [24]. In the revised proposed AD model, A β does not directly cause cognitive symptoms; however, as a dominant driver of downstream pathological processes, it is central to disease pathogenesis [25-27]. Amyloid- β is widely considered as a pathological marker of AD rather than a risk factor [27].

In addition, one of the pathological hallmarks of AD, oxidative stress, is considered both a cause and a consequence of neuroinflammation [28, 29]. As the antioxidant properties of polyphenols have been widely studied, it has become clear that their mechanisms of action go beyond the modulation of oxidative stress [30]. Indeed, several *in vitro* and *in vivo* studies have repeatedly reported that A β production, oxidative markers and neuroinflammation are attenuated by the administration of different polyphenolic compounds with pleiotropic properties (*e.g.* curcumin) [31].

The gene encoding the beta-amyloid precursor protein has been assigned to human chromosome 21 [32]. Thies and Bleiler reported that less than 1% of AD cases are caused by dominantly inherited genetic mutations in genes including APP, PSEN1, and PSEN2 [33]. Inheriting any of these genetic mutations accelerates A β production, leading to AD development before age 60, which is commonly referred to as early-onset familial AD (EO-FAD) [34]. The only gene consistently associated with sporadic late-onset AD (LOAD) across multiple genetic studies, is the apolipoprotein E (APOE) gene [9], where APOE also regulates amyloid- β (A β) metabolism, aggregation, and deposition [34]. Histological analyses of AD brains reveal that APOE is codeposited with A β in amyloid plaques [35], indicating a direct association between APOE and A β in AD pathogenesis [34]. Moreover, APOE ϵ 4 is the most prevalent genetic risk factor for AD, and it is notable that one of its functions appears to directly mediate the accumulation of intracellular A β [1]. The sequence of pathogenetic steps in familial forms of Alzheimer disease (FAD) was proposed [36, 37].

Despite decades of research, no drugs capable of slowing down the progression of Alzheimer's disease have been identified [38]. Hence, the hypothesis that amyloid- β deposits in the brain cause Alzheimer's disease is under pressure to deliver an effective therapy, as well as to explore alternative approaches [38, 39]. Yet, statistical studies show that if scientists today can delay AD onset by five years, the number of current sufferers would be reduced by nearly half in less than a generation. Better still, if AD onset can be delayed by a decade or so, over 90 percent of current patients might die of old age rather than from this disease. It is clear that the goal of delaying and/or mitigating AD is certainly promising.

In this review, we first report on AD treatment strategies which focus almost exclusively on green chemistry (natural polyphenol molecules) and more particularly on those targeting A β production, followed by A β aggregation. We further argue that this family of compounds may yet be part of a cure, as the results of targeted green phenolic molecules

whose properties make them potential candidates for mitigating AD would suggest.

Indeed, polyphenols have been used in other industries in which interesting analogies in the context of neurodegenerative disease may be drawn. Two examples include tannins which were shown to have a dispersive effect on silica nanoparticles aggregates, both in the absence and presence of divalent metal ions (*e.g.* Ca, Mg and Fe), which minimize the propensity of precipitation in the bulk solution, and subsequently decrease the deposition risks on surfaces [40]; and corilagin and another tannin molecule, tannic acid (TA), which have been used as cofactors to induce aggregation/flocculation, or control the stability of microcrystalline cellulose (MCC), using a poly(ethylene oxide) (PEO)/cofactor system [41]. The PEO/cofactor (ligand) association works very well in the presence of salt [42], including physiological solutions. The optimum PEO/corilagin (ligand) dosage, at which the flocculation rate is maximum, was found to be roughly one-tenth of the optimum PEO/TA dosage [41].

2. BIOCHEMICAL ASPECTS OF A β ₄₀ AND A β ₄₂ INVOLVED IN ALZHEIMER'S DISEASE

A β is found in lengths varying from 39 to 43 peptides in A β plaques, with two dominant species: A β ₄₀ and A β ₄₂. A β ₄₂ oligomers are known to be more neurotoxic and more aggregative than A β ₄₀ at comparable concentrations. The production of A β ₄₀ and A β ₄₂ requires the proteolytic processing of fully-modified and glycosylated amyloid precursor protein (APP) by α -secretase, β -secretase (BACE) and γ -secretase [43], and enters a dynamic equilibrium between soluble and deposited forms [37, 44]. Amyloid- β (A β) is generated by neurons, microglia, and astrocytes in the brain, and by platelets, skin fibroblasts, osteoblasts, and skeletal muscle cells in the periphery [45]. If proteolysis occurs at the site of α -secretase action, A β cannot be generated; however, a smaller fragment (P3, A β ₁₇₋₄₀ or A β ₁₇₋₄₂) is produced [18]. When the amyloidogenic APP processing pathway involves cleavages by β - and γ -secretases, it results in the generation of a long-secreted form of APP (sAPP β), C-terminal fragments (CTF 99 and CTF 89) and A β s [43]. This predominantly produces A β ₄₀, and the more amyloidogenic A β ₄₂, at a ratio of roughly 10:1, respectively [1]. A β ₄₂ has two additional hydrophobic residues (Ile41 and Ala42) at the C-terminus, which is more hydrophobic and has a greater propensity to form fibrils than A β ₄₀ [46]. The A β ₄₀ shows significant kinetic solubility, while A β ₄₂ nucleates much more rapidly [46]. The insoluble A β in AD brain tissue is often predominantly A β ₄₂ [47]. The predicted solubility is 0.4 μ M for A β ₄₀ and 0.04 μ M for A β ₄₂ [48], which is consistent with the experimental solubility of 0.04 μ M for A β ₄₂ [49].

In addition, due to their importance and size, both A β ₄₀ and A β ₄₂ have been the subjects of extensive computational studies. A large ensemble of discrete molecular dynamics (DMD)-derived A β ₄₀ and A β ₄₂ monomers and dimers was subjected to fully atomistic molecular dynamics (MD) simulations, where the free energy landscape of A β ₄₂ dimers indicated a larger conformational variability in comparison to that of A β ₄₀ dimers [50]. Côté *et al.* [51] determined the equilibrium structures of A β ₄₀, A β ₄₂, and A β ₄₀ (D23N)

monomers using an accurate coarse-grained force field coupled to Hamiltonian-temperature replica exchange molecular dynamics simulations. They observed that even if these three alloforms are mostly disordered at the monomeric level - in agreement with experiments and previous simulations on A β ₄₀ and A β ₄₂ - striking morphological differences exist [51]. They also showed that A β ₄₂ dimer has a higher propensity than A β ₄₀ dimer to form β -strands at the central hydrophobic core (residues 17-21) and C-terminal (residues 30-42), two crucial segments in A β oligomerization [52]. Nevertheless, and despite considerable work over the past decade, there is still no consensus on the small assemblies - dimers, trimers, etc. - for these two species.

3. OLIGOMERS, PROTOFIBRILS, FIBRILS, FIBERS, AGGREGATES, CLUSTERS, AND PLAQUES

Nasica-Labouze *et al.* have reviewed what the various experiments and computer simulations reveal about the A β protein and its link to AD [53]. Knowledge of A β ₄₀ and A β ₄₂ structures, fibrils, protofibrils, and large oligomers has markedly increased in recent years, and it is clear that polymorphism is present in all steps from monomer to fibrils [53]. The hierarchy of structure from the A β peptide folded into a β -pleated sheet structure through protofilaments to amyloid fibrils was reported by Serpell [54]. In the evolution process from oligomers to protofibrils and then mature fibrils, the oligomers are closely associated with cell toxicity, although it occurs in the early stages of the aggregation process. The water-soluble A β (wsA β) was present in AD brains in the form of monomers and oligomers ranging from less than 10 kDa to greater than 100 kDa [55], suggesting that A β oligomers of various sizes are associated with the disease [56]. AD brains contained six times more wsA β than control brains [55]. The amount of wsA β ₄₂ in AD brains is approximately 50 times greater than the level of soluble A β ₄₂ found in the cerebrospinal fluid (CSF) of AD patients [55]. It was also reported that the formation of an oligomeric, α -helix-containing assembly is a key step in A β fibrillogenesis [57]. The pH dependence of helix formation suggested that Asp and His exerted significant control over this process as well as fibrillogenesis [57].

Using single touch Atomic Force Microscopy (AFM), monomeric A β ₄₂ showed two distinct types of oligomers, low molecular weight (MW) oligomers (~20kD, tetramer) with heights of 1-2nm and high MW oligomers (~56kD, dodecamer) with heights of 3-5nm [58]. In both cases, the oligomers are disc-shaped with diameters of 10-15 nm [58]. Using a predictive coarse-grained protein force field, Zheng *et al.* [48] computed and compared the free energy landscapes and relative stabilities of A β ₄₂ and A β ₄₀ in their monomeric and oligomeric forms up to the octamer. Several A β peptides, linked together through hydrogen bonds, lead to the formation of protofibrils (25-30 Å), comprised of short beta sheets along their width with aligned strands along the lengths.

Aggregation of several protofibrils generates structures called fibrils (60-80 Å) while further aggregation of these fibrils generates A β plaques. Protofibrils formed from A β ₄₀ and A β ₄₂ show flexible fibers roughly 60-100 Å in diameter [59]. A β ₄₂ fibrils formed more rapidly than A β ₄₀ fi-

brils [54]. Detailed comparison of the A β ₄₂ and A β ₄₀ fibril structures reveals that they share an axial twofold symmetry and a similar protofilament structure [60]. Amyloid fibrils are typically 5-15 nm in width, unbranched, straight over length scales approaching 1 micron, and often many microns long [49]. The spacing between β strands in a β sheet is 0.46-0.48 nm [49]. Therefore, a one micron length of amyloid fibril typically contains thousands of protein molecules, with the exact number dependent on the number of cross- β subunits, the number of β strand segments contributing to each cross- β subunit by one molecule, and the number of β sheet layers within each subunit [49]. The structure of amyloid fibrils resembles an aircraft cable, in which 3-6 filaments wrap around one another to form the fibril [10]. The individual filaments have a lamellar cross- β -sheet structure, composed of thousands of individual non-covalently associated protein or peptide subunits. Amyloid fibrils are inherently non-crystalline, insoluble materials; this renders it difficult to determine their high-resolution molecular structures when using traditional methods, particularly x-ray crystallography and multidimensional Nuclear Magnetic Resonance (NMR) spectroscopy [49].

An A β fibril has a U-shaped conformation with the β -strands formed by the hp1, hp2 and C-term segment [61]. Initial work by Tjenberg identified the A β central hydrophobic core KLVFF as the key scaffold for designing disrupters of A β ₄₀ fibrillization [62]. They also showed that peptides incorporating a short A β fragment (KLVFF ; A β ₁₆₋₂₀) can bind full-length A β and prevent its assembly into amyloid fibrils [63]. Bett *et al.* investigated the effect of modifying the KLVFF hydrophobic core of A β by replacing N- and C-terminal groups with various polar moieties, which were found to alter the formation and structure of amyloid fibrils and sometimes induced the disassembly of preformed fibrils [64]. Polymorphism is an important property of amyloid fibrils [65]. Different A β ₄₀ fibril morphologies also showed significantly different toxicities in neuronal cell cultures [66]. Moreover, A β ₄₀ fibril in cultures of primary rat embryonic hippocampal neurons are neurotoxic at A β ₄₀ concentrations of 10 μ M or above [66].

The electrochemical detection and kinetics of the aggregation of amyloid beta peptides (A β ₄₀, A β ₄₂) using three different voltammetric techniques, after incubation at 80 μ M, were investigated [67]. There are several kinds of aggregates, including disordered or amorphous aggregates, but amyloid fibrils are most characteristic [68]. Hu *et al.* proposed the aggregation mechanisms of A β ₄₂, with and without nuclei, where aggregation/ disaggregation equilibrium is occurring [69]. During the A β aggregation process, soluble A β peptides are known to change their conformation into a β sheet structure and form nuclei (lag phase). This further accelerates the fibrillogenesis process to form insoluble fibrils with enriched β sheet structures as "seed" (elongation phase) [46, 70]. Harper and Lansbury suggested the nucleation-dependent polymerization mechanism, which dictates this aggregation, is a function of protein concentration and time [70]. The characteristic features of a simple nucleation-dependent polymerization are as follows: (a) no aggregation occurs at a protein concentration below the critical concentration; (b) at protein concentrations which exceed the critical concentration by a small amount, there is lag time before

polymerization occurs; (c) during this lag time, the addition of a seed leads to immediate polymerization [71]. Under “physiological” conditions (pH 7-8, 5-100 μM salt, 25-37 $^{\circ}\text{C}$), the experimental qualitative consensus includes: (a) $\text{A}\beta_{40}$ rapidly forms amyloid fibrils at concentrations over 100 μM [72, 73]; and (b) at $\text{A}\beta_{40}$ concentrations between 20 μM and 80 μM , a period of kinetic solubility precedes fibril formation [74, 75]. The critical concentration of $\text{A}\beta_{42}$ appears to be in the low micromolar range, *ca.* fivefold lower than the critical concentration of $\text{A}\beta_{40}$ [70]. The lag time for aggregation was decreased by a physiological NaCl concentration of 150 mM, the same condition that induces protofibril association [76]. Salt-induced aggregation has also been observed; *e.g.* NaCl at concentrations ranging from dozens to hundreds of millimolars can promote the lateral association of 70 μM $\text{A}\beta_{40}$ protofibrils [76]. Recently, a coarse grain model was used to investigate the aggregation of 75mer $\text{A}\beta_{42}$ oligomer, and the salt effect [69].

4. STRATEGIES FOR AD TREATMENT

The complexity of $\text{A}\beta$ production and aggregation pathways, and the unknowns regarding the role of the various structures in the development of AD, partly explain the remaining challenges in finding a treatment to slow or prevent this disease. Clearly, there remains a need to work on a fundamental understanding of $\text{A}\beta$'s kinetics as well as on possible inhibitors that may act at various points along the pathway to toxicity.

4.1. Therapeutic Strategies for Decreasing $\text{A}\beta$ Production

There are at least three paths to reducing $\text{A}\beta$ production: inhibiting β - or γ -secretase, and enhancing α -secretase activity [43]. To ensure transport to the active site, enzyme inhibitors with therapeutic potential should preferably be smaller than 700 Da [77].

4.2. β -Secretase (BACE) Inhibitor

β -site amyloid precursor protein cleaving enzyme 1 (BACE1), a β -secretase enzyme required for the production of the neurotoxic β -amyloid ($\text{A}\beta$) peptide, plays a crucial early role in AD etiology [78]. β -secretase has 501 amino acid (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 [79]. BACE is expressed at higher levels in neurons than in glia [79]. This supports the idea that neurons are the primary source of extracellular $\text{A}\beta$ deposited in amyloid plaques [80]. It was reported that BACE1 accumulates in swollen presynaptic neuronal structures that surround amyloid plaques in AD and APP transgenic brains [81, 82]. A BACE1 homolog named BACE2 cleaves APP into a short peptide. However, BACE2 is present in small quantities in the brain, and thus, this enzyme is likely not crucial in $\text{A}\beta$ peptide formation [83]. BACE activity increases significantly with age in mouse, monkey, and human brains (18-92 years of age) [84]. BACE protein levels, however, did not change with age, suggesting that an age-related increase of BACE activity contributes to the increased production and accumulation of $\text{A}\beta$ in the brain, and potentially predisposes humans to Alzheimer's disease [84]. However, to date the

pharmaceutical industry has been hard-pressed to design BACE1 inhibitor drugs able to cross the blood-brain barrier.

4.3. α -Secretase Activator

Enhancing the possibility of α -cleavage through the activation of α -secretase has been reported as an effective approach for decreasing production of the $\text{A}\beta$ monomer and promoting the generation of soluble APP fragments to protect neurons [18, 85].

4.4. γ -Secretase Inhibitors and Modulators (GSM)

The inhibition of γ -secretase is another logical target. γ -secretase is a nucleoprotein complex containing at least four different proteins. Of these, presenilin PS-1 and PS-2 appear to be responsible for the enzymatic action on APP [85]. Unfortunately, aside from APP, γ -secretase has many other substrates and cleaves several other transmembrane proteins including the notch receptor-1, necessary for growth and development [85]. γ -secretase cuts C99 to release $\text{A}\beta$, which is secreted from the cell [78, 86, 87]. Interestingly, the γ -secretase cut is imprecise and creates $\text{A}\beta$ isoforms of different lengths at the carboxy (C) terminus, whose longer isoforms are strongly associated with AD [78].

4.5. Therapeutic Strategies for Preventing $\text{A}\beta$ Aggregation

Given the difficulty of controlling $\text{A}\beta$ production β , considerable efforts have been made to prevent $\text{A}\beta$ aggregation through a wide range of potential inhibitors.

4.6. Phenolic-Based non-Peptidic Anti-Aggregation

One strategy to mitigate AD may be the development of neuroprotective agents capable of reducing the $\text{A}\beta$ aggregation process and/or inducing the formation of non-toxic $\text{A}\beta$ oligomers [88]. Since amyloid peptides are located in the brain, an effective drug and/or its metabolites should be able to cross the blood-brain barrier [89] and reach the central nervous system (CNS). Researchers have investigated the interaction between polyphenols and the BBB [90], as well as the permeability of flavonoids and their known metabolites across the BBB [91-93]. Many natural molecules, extracted from plants and trees (green chemistry) display the key characteristics and properties (*e.g.* hydrophobicity, aromaticity and hydrogen bonding) necessary to maximize the chances of mitigating Alzheimer's disease. These include the fact that their metabolites can cross the BBB, exhibit a hydrophobic functional character, and associate with protein. In addition, the resulting molecular complexes show a colloidal behavior (in terms of stability and kinetics of association). Some are present in wine or are already used in medicine due to their low toxicity. They can alter the nucleation process of formation of protofibril/fibril/fiber, hence minimizing or altering aggregate/cluster/plaque structures and cytotoxicity.

These polyphenols represent a large potential drug reservoir for fighting Alzheimer's disease. More than 8,000 polyphenolic compounds have been identified in foods [83, 94]. Flavonoids form the largest polyphenol group, with more than 5,000 flavonoid compounds widely distributed in plants [95]. Most of the flavonoids are attached to sugars

(glycosides), although they are occasionally found as aglycones [95].

Polyphenols are powerful anti-amyloidogenic due to physicochemical features such as the presence of aromatic rings, molecular planarity, the 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, *e.g.* reducing amyloid load [96-98]. Polyphenols and their derivatives, as well as curcumin, showed anti-aggregation activity [99]. Non-flavonoids showed higher anti-aggregation activity than flavonoids. Lakey-Beitia *et al.* [83] proposed a relationship between polyphenol structure and anti-aggregation activity, in which polyphenols with more aromatic rings, planarity, and hydroxyl and keto groups might exhibit the largest inhibition activity. Stronger BACE1 (β -secretase) inhibitor activity appeared to be related to the pyrogallol moiety on C-2 and/or C-3 of the catechin skeleton, while the C-2 and C-3 stereochemistry had no effect [77].

Water-soluble tannins have molecular weights between 500 and 3,000 Da, and are widely distributed in nearly all plant foods and beverages [100]. Tannins can be defined as a unique group of phenolic metabolites of relatively high molecular weight, with the ability to complex strongly with carbohydrates and proteins [100]. However, some tannins are not water-soluble compounds; some have molecular weights ranging from 3,000 to over 30,000 Da. Tannins can be divided into two major groups, hydrolysable and condensed tannins. The former involves two types of tannins, gallotannins and ellagitannins. Tannases are key enzymes in the degradation of gallotannins. Tannins have the highest number of hydroxyl groups among polyphenolic compounds and some of the strongest anti-aggregation activity [101, 102]. The main physicochemical properties of molecules with the potential to inhibit amyloid fibril formation might be induced by the presence of aromatic rings and the ability to form non-covalent interactions with amino acid residues of the A β peptide sequence [97, 98]. Moreover, inhibitor planarity is essential for increasing surface contact with A β peptides [96]. Most polyphenols have more than two aromatic rings, essential for π - π stacking interactions with hydrophobic amino acid residues of A β (Tyr, Phe), and at least three hydroxyl groups that form hydrogen bonds with hydrophilic amino acid residues of A β (His6, Ser8, Tyr10, His14, Lys16) [103].

Ellagitannins are a biologically and structurally diverse class of natural products. The structure typically consists of galloyl and hexahydroxydiphenoyl (HHDP) group(s) esterified to a glucose. Their structural diversity arises from the number and location of the ester substituents, modification of the substituents, oligomerization, and ring-opening of the pyranose [104].

5. CURCUMIN

First isolated in 1815, curcumin is extracted from turmeric, a spice derived from the rhizomes of *curcuma longa* which belongs to the zingiberaceae (ginger) family [105]. Native to the monsoon forests of south-east Asia, turmeric is a perennial herb commonly used in Indian, Asian and Middle Eastern foods [106]. Research over the last half-century has

revealed several important functions of curcumin [107]. Goel *et al.* [107] reported a comprehensive review of the literature, including a list of molecular targets and ligands which interact with curcumin [99]. Curcumin showed a wide range of pharmacological activities such as anticancer [108], antioxidant [109, 110], antiinflammatory [111, 112], antiangiogenic [113] and wound-healing effects [114]. Curcumin metabolites, *e.g.* biotransformed to dehydrocurcumin (DHC) and tetrahydrocurcumin (THC), are subsequently converted to monoglucuronides conjugates [115]. Curcumin differs from THC which lacks α,β -unsaturated carbonyl moiety and is white in color, and is bioavailable after administration in animals [116]. Interestingly, Aggarwal *et al.* [116] reported several biological activities, including studies showing curcumin to be more active than THC and other studies showing THC to be more active than curcumin. Both phenolic OH and the β -diketone moiety of curcumin are responsible for the antioxidant effects, a function of the type of radical [117]. Aggarwal *et al.* [118] further suggested that curcumin may mediate its effect against AD through eight mechanisms. Those directly related to anti-aggregation and/or disaggregation are: i) curcumin can modulate the formation, extension, and destabilization of fA β ₄₀ and fA β ₄₂ *in vitro* [101]; ii) it could inhibit aggregated as well as disaggregated fA β ₄₀ [99]; and iii) it labels amyloid pathology *in vivo*, disrupts existing plaques, and partially restores distorted neurites in an AD mouse model [119].

A recent review of curcumin's mechanisms of action in AD suggests its usefulness as a therapeutic agent may be hindered by its low bioavailability [107, 120], and low solubility [29], *e.g.* 0.0004 mg/ml at pH 7.3 [121], compatible with lower than 0.001 mg/ml at pH 6.96 [122]. Although 10 or 12 g of curcumin administered orally in humans showed curcumin levels in serum to be approximately 50 ng/ml, this resulted in a minimum bioavailability of curcumin in the blood circulation to achieve its therapeutic effects [123]. Consequently, significant efforts were made to increase curcumin solubility, bioavailability and stability [121, 122], *e.g.* the formation of cyclodextrin/curcumin complexes leading to an increase in curcumin's water solubility by a factor of at least 10⁴ at pH 5 [124]. Other ways of increasing bioavailability include making nanoparticles [125]; for example, NanoCurc, a nanoformulation of curcumin, showed neuroprotective and neurorescue effects in neuronal cultures and animals [126].

Among 214 tested compounds, curcuminoids, flavone-type flavonoids, and naphthoquinones were shown to be potent inhibitors of A β fibrilization *in vitro* [127]. Curcumin binds to the N-terminus (residues 5-20) of A β ₄₂ monomers [58]. The hydrophobic C-terminus of A β ₄₂ has long been considered important in driving fibril formation [46]. Curcumin directly binds with small amyloid- β species to inhibit aggregation and fibril formation *in vitro* and *in vivo* [99], and to destabilize preformed fibrils at concentrations between 0.1 μ M and 1.0 μ M [101, 128]. As A β ₄₂ monitored by UV spectroscopy at 200nm, curcumin's inhibition of A β ₄₂ fibrillization was 49 +/- 9% [129]. Molecular docking revealed curcumin's preferential interaction with the lateral oligomer region, near the 17-21 amino acid residues of A β ₄₀ peptide [130]. Under *in vitro* aggregating conditions, curcumin inhibited aggregation (IC₅₀ = 0.8 μ M), and disaggre-

gated fibrillar A β_{40} (IC₅₀ = 1.0 μ M) [99]. Curcumin was a better A β_{40} aggregation inhibitor than ibuprofen and prevented A β_{42} oligomer formation and toxicity between 0.1 and 1.0 μ M [99]. *In vivo* studies showed that curcumin injected peripherally into aged Tg mice crossed the blood-brain barrier and bound to plaques [99]. Curcumin-treated mice had noticeably fewer and smaller plaques, *i.e.*, a significant reduction in plaque size of about 30% was observed after seven days of treatment [119]. Curcumin treatment (160 ppm) of Tg mice significantly lowered both insoluble amyloid and plaque burden by 39% and 43%, respectively [131].

Curcumin has also been the focus of intense research using a hybridization strategy [132]. Piperine (1-piperoyl-piperidine) is an alkaloid extracted from black pepper fruits (*piper nigrum*) and present also in long peppers (*piper longum*) and other pepper species (*piperaceae*). Piperine is known for its ability to enhance the bioavailability of numerous drugs and phytochemicals [133]. In the context of AD, Suresh and Srinivasan orally administered 500 mg curcumin, 170 mg piperine, or a combination of the two in a single formulation to Wistar male albino rats [134]. They found that when it was administered concomitantly with piperine, curcumin remained in the body tissues significantly longer; moreover, curcumin was detected in the brain up to 96 hours following treatment [134]. A combination diet of dietary supplements in which curcumin and EGCG are the two main components and piperine was also included, not only improved cognitive functioning in transgenic mouse models of AD, but also decreased A β levels and oligomerization [135]. Recently, novel curcumin derivatives were proposed as potent inhibitors against AD, *e.g.* protecting APP from secretase attacks, and consequently inhibiting the production of A β peptides [136]. However, to date the anticipated benefits of curcumin have not been demonstrated in AD clinical trials [106].

6. EGCG

Human epidemiological and animal data suggest that drinking tea may decrease the incidence of dementia, AD and Parkinson's disease [137]. In particular, the main catechin polyphenol constituent found in tea, (-)-epigallocatechin-3-gallate (EGCG), has been shown to exert neuroprotective activities in a wide array of cellular and animal models of neurological disorders [137]. EGCG also inhibits A β aggregation in animal models by activating α -secretase and disrupting unfolded peptide [138]. EGCG markedly promotes cleavage of α -C-terminal APP fragments, and elevates the N-terminal of the APP cleavage product, soluble APP- α [139]. Moreover, it inhibits the formation of A β oligomers, either by binding directly to the protein or possibly by acting on a protein chaperone [138].

An extensive replica-exchange molecular dynamics (REMD) simulation was performed to investigate the progress patterns of EGCG inhibition on the A β_{16-22} hexamer [140]. Both electrostatic and van der Waals interactions were involved in the binding domain. In addition, quantum chemical methods showed that π - π stacking interactions are critical between EGCG and peptides [140]. The polyphenol EGCG efficiently inhibits the fibrillogenesis of amyloid- β by

directly binding to the natively unfolded polypeptides and preventing their conversion into toxic, on-pathway aggregation intermediates. Formation of unstructured, nontoxic amyloid- β oligomers of a new type, rather than β -sheet-rich amyloids, is promoted; this suggests a generic effect on aggregation pathways in neurodegenerative diseases [141]. In addition, EGCG has the ability to convert large, mature amyloid- β fibrils into smaller, amorphous protein aggregates that are nontoxic to mammalian cells, suggesting that EGCG is a potent remodeling agent of mature amyloid fibrils [142]. Phase II/III clinical trials of EGCG have been reported [138].

7. RESVERATROL

The polyphenolic compound resveratrol (3,4',5-trihydroxystilbene), first isolated in 1940 [143], has been found in over 70 plant species, including herbs and human food products such as grapes, berries, and wine [144]. Its concentration is a function of geographical origin, variety, growing methods, and winemaking processes [145]. Moreno-Labanda *et al.* showed that the average total resveratrol equivalent content, as determined in a survey of 45 Spanish red wine types, was about 8 mg/L [146]. Increasing evidence has pointed to resveratrol's usefulness in treating cardiovascular diseases, cancers, pain, and inflammation injuries of the tissues, and in lowering the risk of neurodegenerative disorders such as Alzheimer's disease (AD) [144].

Resveratrol exists in two isomers: trans- and cis-resveratrol. However, little is known about the cis-isomer's pharmacological activity [147]. Resveratrol can induce protective effects in neurodegenerative conditions such as AD [148]. Surface plasmon resonance (SPR) and proton nuclear magnetic resonance (1-H NMR) methods showed direct binding of resveratrol to A β [98]. It was also shown that resveratrol binds to the N-terminus (residues 5-20) of A β_{42} monomers [58]. Resveratrol promotes the non-amyloidogenic cleavage of the amyloid precursor protein, enhances clearance of amyloid beta-peptides, and reduces neuronal damage [138, 144]. Because it has no effect on the A β -producing enzymes β - and γ -secretases, resveratrol does not inhibit A β production; rather, it promotes intracellular degradation of A β *via* a mechanism that involves the proteasome [148]. Neither resveratrol nor its conjugated metabolites were detectable in the brain. Nevertheless, resveratrol diminished plaque formation in a region-specific manner; the largest reductions in percentage area occupied by plaques were observed in the medial cortex (48%), striatum (89%) and hypothalamus (90%) [149]. Karuppagounder *et al.* suggest the concept that the onset of neurodegenerative disease may be delayed or mitigated through the use of dietary chemo-preventive agents which protect against β -amyloid plaque formation and oxidative stress [149]. While resveratrol could dose-dependently inhibit A β_{42} fibril formation and cytotoxicity, surprisingly it did not prevent A β_{42} oligomerization [150]. Feng *et al.* indicate that when added to 10 μ M A β_{42} , 10 μ M and 100 μ M of resveratrol could inhibit over 50% and 90% of A β_{42} fibril formation, respectively [150]. When delivered in combination, the potentially bioactive metabolites from grape seed extracts (GSE), resveratrol, and Concord juice extract can cross the blood-brain barrier and accumulate in the brain [151].

8. TANNIC ACID

Tannic acid (TA), MW = 1701,18 g/mol, is a plant-derived polyphenol found in several herbaceous and woody plants. Tannic acid reduces A β production and inhibits amyloidogenic APP metabolism in neuron-like cells [152]. For example, tannic acid administered orally to transgenic PSAPP mouse models of cerebral amyloidosis for six months raises the possibility that, by inhibiting β -secretase activity and neuroinflammation, and hence mitigating AD pathology, dietary supplementation with TA may be prophylactic for AD [152]. Tannic acid significantly inhibits the aggregation of A β [96, 101]. The effective concentrations (EC₅₀) of TA for the formation, extension and destabilization of β -amyloid fibrils (fA β) are in the order of less than 0.1 μ M, and the IC₅₀ *in vitro* of 0.012 and 0.022 μ M for A β ₄₀ and A β ₄₂, respectively [96, 101].

TA is a large molecular weight molecule that cannot easily penetrate the cellular membrane, or cross the blood-brain barrier [153]. However, numerous studies have focused on gallotannin biodegradation, where certain industrial applications involve the production of tannase, the biotransformation of tannic acid to gallic acid (GA) or pyrogallol, and the detannification of food and fodder [154]. As gallic acid has been reported to cross the BBB in murine models, the GA moiety may be responsible for the bioactivity of TA [128]. Experimental results also suggest that tau peptide interacts with TA by forming a hairpin structure, a feature for inhibiting tau polymerization [155].

9. MORIN

The effective concentrations (EC₅₀) of myricetin, morin, and quercetin for the formation, extension and destabilization of A β fibrils were found to be in the order of 0.1 μ M to 1 μ M [156]. Atomistic, explicit-solvent molecular dynamics (MD) simulations were used to identify the mechanism through which A β fibril is destabilized by morin, an effective anti-aggregation flavonoid [157]. Morin was found to bind to the ends of the fibrils, thereby blocking the attachment of an incoming peptide. It also penetrated the hydrophobic core to disrupt electrostatic interactions between oppositely-charged side chains of Asp23 and Lys28 (*i.e.* a salt bridge interaction) and interfere with backbone hydrogen bonding [157, 158].

9.1. Other Natural Green Molecules (*e.g.* Anthocyanins, Apigenin, Catechin, Gallotannins, Gallic Acid, Lisetin, Luleolin, Myricetin, Oleuropein, Quercetin, and Rutin)

Gallotannins such as hexagalloylglucopyranose and galloylated glucose derivatives all inhibit A β aggregation *in vitro*, and monogalloylated alpha-glucogallin and a natural beta-hexagalloylglucose are reported to be the strongest inhibitors [129]. However, the neuroprotective effects of gallic acid (GA) derivatives appear to be more dependent on their molecular polarities than on antioxidant activities in the human SH-SY5Y cell line [159].

Rutin is a common name for the flavonoid glycoside (quercetin-3-O-rutinoside), which is composed of the quercetin aglycone and rutinoside sugar units [160]. Rutin draws its name from its main source plant, *Ruta graveolens*, from which it was first isolated in 1842. Isolation of this com-

pound from various plants (*e.g.* the elder plant, or *Sambucus canadensis* L) was also described as far back as the early 20th century [161]. Rutin has a molecular weight of 610.52 g/mol and its solubility in water is 0.13 g/L. Sabogal-Guáqueta *et al.* [162] showed that quercetin decreases extracellular β -amyloidosis, supported by a significant reduction in the paired helical filament (PHF), A β ₄₀ and A β ₄₂ levels as well as a decrease in BACE1-mediated cleavage of APP (into CTF β). It was also suggested that rutin's effectiveness in preventing cognitive deficits might be beneficial in the treatment of sporadic dementia of Alzheimer type (SDAT) [163].

Several MD trajectories were analyzed, describing the evolution of the GNNQQNY heptapeptide decamer fragment taken from its crystal structure, both singly and in the presence of myricetin and kaempferol, two naturally-occurring polyphenols found to be strong and weak aggregation inhibitors, respectively [164]. The binding affinity of A β ₄₀ and A β ₄₂ peptides with 342 compounds derived from Vietnamese plants was investigated using a docking technique combined with the molecular mechanic Poisson-Boltzmann surface area method [89]. Of these compounds, only five ligands showed a high binding affinity to monomers and mature fibrils of amyloid peptides, including one flavone, hinokiflavone [89]. Oxidized flavonoids generally inhibited A β ₄₀ fibril formation considerably more potently than fresh compounds [97]. A significant decrease in the rate of fibril extension was observed when more than 0.5 μ M myricetin was injected into the surface plasmon resonance (SPR) experimental system [97].

Rigacci *et al.* [165] reported that the oleuropein polyphenol eliminates the appearance of early toxic oligomers, favoring the formation of stable harmless protofibrils, which are structurally different from typical A β ₄₂ fibrils. They also showed that oleuropein aglycon is most effective when present at the start of the aggregation process [165]. These findings suggest that flavonoids, and particularly myricetin, exert an anti-amyloidogenic effect *in vitro* by preferentially and reversibly binding to the amyloid fibril structure of fA β , rather than to A β monomers [97]. Myricetin, which dose-dependently inhibits BACE1 with an IC₅₀=2.5 μ M [166], was supported by molecular modeling where van der Waals interactions were the main driving force guiding ligand-induced conformational switching to the closed conformer [167]. Natural flavonoids act as non-peptidic BACE-1 inhibitors. The calculated 50% inhibitory concentrations (IC₅₀) were as follows; myricetin (2.8 μ M) < quercetin (5.4 μ M) < kaempferol (14.7 μ M) < morin (21.7 μ M) < apigenin (38.5 μ M) [166]. Moreover, the polyphenols' anti-amyloidogenic and fibril-destabilizing activity may occur in the following order: myricetin (Myr) = morin (Mor) = quercetin (Qur) > kaempferol (Kmp) > (+)-catechin (Cat) = (-)-epicatechin (epi-Cat) [156].

Interestingly, results showed that grape flavonoid pigments, *e.g.* anthocyanins, can reach the mammalian brain within minutes of their introduction into the stomach [168]. A diet enriched in blueberries, a fruit rich in anthocyanins, prevents cognitive deficits in APP/PS1 transgenic mice with no alterations in A β deposits [169]. A recent review showed that terminalia chebula extracts and its constituents have

acetylcholinesterase inhibitors (AChEIs) and antioxidant and anti-inflammatory effects, all of which are relevant in the treatment of Alzheimer's disease [170].

9.2. Green Chemistry

9.2.1. Polyphenol Intermediate Size Anti-Aggregation

To expand the number of polyphenol candidates in AD treatment, it is useful to examine their industrial applications. For example, some polyphenols (*e.g.* tannins) used in the corrosion inhibition and paper industries display remarkable dispersive effects on silica nanoparticle aggregates [40]; in addition, as cofactors they induce aggregation, or control the stability of microcrystalline cellulose (MCC) [41], which may be relevant in A β aggregation.

To demonstrate this potential interest, we considered two potential TA metabolites, TGG (1,3,6-tri-O-galloyl- β -D-glucose) and GA (Fig. 1). Moreover, (Fig. 2) shows the molecular structure of corilagin (β -1-O-galloyl-3,6-(R)-hexahydroxydiphenoyl-D-glucose), a close analogue of TGG. Tannins are also known for their strong affinity for proteins, as they form tannin/protein complexes leading to either enzyme deactivation or protein insolubility. For example, nineteen phenolic compounds exhibited strong inhibition against prolyl endopeptidase (PEP), an enzyme that may play a functional role in amyloidogenesis in the brain [171]. Of those, TGG ($IC_{50} = 157.2 \times 10^{-9}$ M) and corilagin ($IC_{50} = 236.5 \times 10^{-9}$ M) exhibited strong inhibition against PEP [172] (Table 1). These molecules share many of the properties observed in molecules presented in the previous sections, suggesting that naturally-occurring polyphenols should be more extensively studied in the context of AD. These molecules are also interesting because they are natural green polyphenols extractable through green chemistry, and act as cofactors in the association of macromolecules. The molecular structures of TGG and corilagin were determined using the predictive PM3 Semiempirical Molecular Orbital Theory, since the theoretical values parallel experimental results [173, 174]. They have a more flexible molecular structure (TGG) and a rigid one (corilagin), respectively [175, 176].

With a molecular weight of 636.46 g/mol, TGG (1,3,6-tri-O-galloyl- β -D-glucose) can be found in *terminalia chebula* (Black or chebulic myrobalan) and *paeonia lactiflora*. It was characterized using NMR spectroscopic methods [178]. With 69 atoms and 120 filled delocalized molecular orbitals (DLMOs), TGG has three possible conformers, *e.g.* TGGT, which represents a tripod-like molecular structure [175,

176]. The size of the TGGT cavity is large enough to contain a segment of the amyloid-beta (A β) protein [175, 176]. Surprisingly, TGG's experimental solubility in water does not appear to have been reported in the literature. Nevertheless, the calculated solubility of TGG is 1.6 mg/ml at pH 5-7 and 25°C (using Advanced Chemistry Development (ACD/Labs) Software V11.02 (©1994-2019 ACD/Labs)).

Corilagin (β -1-O-galloyl-3,6-(R)-hexahydroxydiphenoyl-D-glucose) has a molecular weight of 634.45 g/mol and is one of the 1C4/ β -ellagitannins. It is the first discovered natural product containing stable axial-rich glucose [179]. While it was first isolated from dividivi (*Caesalpinia coriaria*) in 1951 [179, 180], its first full synthesis was only reported in 2008 [104]. It can also be extracted from several woodland trees from the African savannah *terminalia laxiflora* [180] and *macroptera*, as well as from *Geranium sibiricum* [181, 182]. Recently, Li *et al.* [182] reported that corilagin has been identified in as many as 53 plants worldwide. Corilagin's solubility has not been clearly defined in the literature. For example, at pH 5.0 its solubility in aqueous solution is at least 0.005 mg/ml [41]. Considering that the solubility of phenolic molecules (such as corilagin) increases with pH, corilagin's solubility is significantly higher than that of curcumin (0.0004 mg/ml at pH 7.3 [121]). Theoretical molecular modeling showed that with 67 atoms and 119 filled DLMOs, corilagin has two joined phenolic rings (R3-R6); this results in three conformations, namely boat, skew-boat, and chair, with final heats of formation of -645.61, -629.09 and -623.57 kcal/mol, respectively [175, 176]. The difference in the final heat of formation between the boat and skew-boat conformers (16.52 kcal/mol) indicated that corilagin has a more stable boat conformation [175, 176]. Nuclear magnetic resonance of corilagin showed the glucopyranose ring has a unique boat conformation [183, 184], in agreement with the calculations [175, 176] using the semiempirical PM3 method [173, 174]. Corilagin may interact with the amyloid-beta (A β) protein, where the cavity ranges from 5.8 to 14.1 Å [175, 176] (Fig. 2).

Corilagin, a hydrolyzable tannin, demonstrates a wide spectrum of pharmacological properties [182], including usefulness in antioxidant [181, 185], anti-hypertensive [186, 187], anticancer / antitumor [182, 188], anti-inflammatory [188-192], and antibacterial/antiviral [193-196] treatments (Table 1). It is also a potential treatment for radiation-induced brain injuries (RIBI) [197, 198], as well as in Type II diabetes management [182, 199]. Moreover, corilagin may inhibit the growth of various microorganisms, including bac-

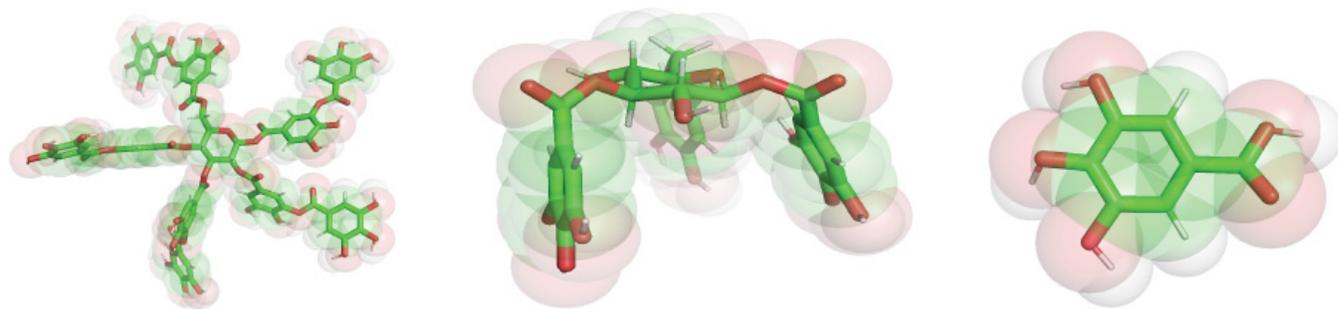


Fig. (1). Molecular structures of phenolic molecules: left) top view of one possible structure of tannic acid (TA) [177]; middle) TGG (1,3,6-tri-O-galloyl- β -D-glucose); and right) gallic acid (GA). This shows potential metabolites of TA, *e.g.* TGG and GA (adapted from Ref. [176]).

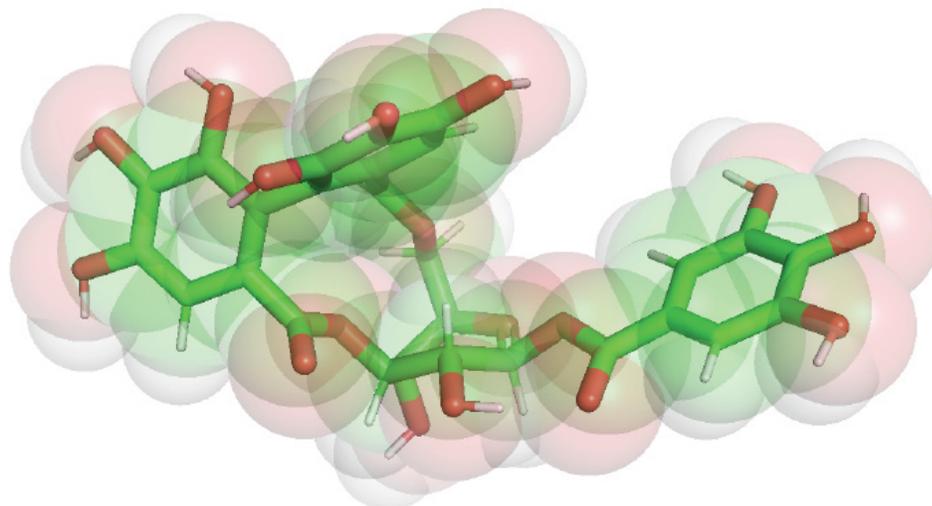


Fig. (2). Molecular structure of corilagin (β -1-O-galloyl-3,6-(R)-hexahydroxydiphenoyl-D-glucose), a close analogue of TGG as shown in Figure 1 (adapted from Ref. [176]).

Table 1. Pharmacological properties of natural polyphenols (curcumin, corilagin, and TGG).

Pharmacological Properties	Curcumin	Ref.	Corilagin	Ref.	TGG	Ref.
Anticancer / Antitumor	X	[108]	X	[182, 188]	-	-
Antioxidant	X	[31, 109, 110]	X	[181, 185]	X	-
Anti-inflammatory	X	[111, 112]	X	[188–192]	-	-
antihypertensive	-	-	X	[186, 187]	-	-
Antibacterial / antiviral	-	-	X	[182, 193–196]	-	-
Antiangiogenic	X	[113]	X	-	-	-
Wound healing	X	[114]	-	-	-	-
Managing Type II diabetes	-	-	X	[182, 199]	-	-
Radiation-induced brain injury (RIBI)	-	-	X	[197, 198]	-	-
Anti-amyloid	X	[31]	X	[182]	-	-
Other	X	[107, 116]	-	[172, 182]	X	[172]

teria, fungi, and viruses [182]. The cytotoxicity of corilagin was tested using the XTT assay; the 50% cytotoxic concentration of corilagin for African green monkey kidney (Vero) cells was $37.4 \pm 6.7 \mu\text{M}$ [200]. It was suggested that corilagin exerted almost no toxicity on normal cells or tissues [182].

Corilagin extracted from *Geranium thunbergii* not only inhibited recombinant human β -secretase (BACE1) activity, but also noncompetitively bound with and suppressed BACE1 in a silico docking model system [201]. Two compounds, geraniin and corilagin, isolated from the most active

EtOAc fraction of *G. thunbergii*, exhibited predominant *in vitro* inhibition against β -secretase, with IC_{50} values of 4.0×10^{-6} and 3.4×10^{-5} M, respectively [201]. Both compounds exhibited no significant inhibition against α -secretase and other serine proteases including trypsin and chymotrypsin, indicating they were relatively specific and selective inhibitors of β -secretase [201]. Recently, Youn *et al.* [192] studied the underlying molecular mechanisms responsible for the neuroprotective effects of corilagin against $\text{A}\beta_{25-35}$ -triggered neurotoxicity and inflammatory responses in PC12 cells. Pretreatment with corilagin before exposure to $\text{A}\beta_{25-35}$ increased cell viability in a dose-dependent manner

by 68.67%, 80.78%, and 90.87% at 0.1 μM , 1 μM , and 10 μM , respectively [192]. These findings suggest that attenuation of $\text{A}\beta_{25-35}$ -induced inflammatory responses by downregulating the NF- κB signaling pathway might be a valuable strategy in both Alzheimer's disease prevention and/or treatment.

Guo *et al.* [191] studied the anti-inflammatory effect of corilagin in herpes simplex virus (HSV-1)-infected microglial cells and an HSV-1-infected mouse brain. Here, the brain of the animal model treated with corilagin displayed a significant decrease of herpes simplex encephalitis-induced pathological changes. Interestingly, Yeo *et al.* [196] investigated the antiviral effect of corilagin and *Phyllanthus urinaria* extract (which contains corilagin as a major component) against human enterovirus 71 and Coxsackievirus A16 *in vitro*. Their findings revealed that corilagin reduces the cytotoxicity induced by EV71 or CA16 on Vero cells with an IC_{50} value of 5.6 and 32.33 $\mu\text{g}/\text{mL}$, respectively [196]. *Phyllanthus amarus* extracts potently inhibit HIV-1 replication in HeLa CD4^+ cells with 50% effective concentration values (EC_{50}) ranging from 0.9 to 7.6 $\mu\text{g}/\text{ml}$ [194]. A gallotannin-enriched fraction showed enhanced activity (0.4 $\mu\text{g}/\text{ml}$), with the purified gallotannins geraniin and corilagin being most active (0.24 $\mu\text{g}/\text{ml}$) [194]. Corilagin isolated from medicinal plants, such as *Phyllanthus amarus* and *Caesalpinia coriaria*, were shown to attenuate radiation-induced brain injuries in mice [198]. Morris water testing indicated corilagin improved the neurocognitive deficits in RIBI mice [198]. In addition, microglia play a major role in pathological events leading to inflammation-related diseases, such as radiation-induced brain injuries, Alzheimer's disease, and multiple sclerosis [197]. Data from Dong *et al.* [197] suggest that corilagin inhibits activation of radiation-induced microglia through suppression of the NF- κB pathway, indicating the compound's viability as a potential RIBI treatment.

To summarize, these green molecules (*e.g.* TGG and corilagin) have very similar molecular structures and properties, including three phenolic rings for π - π stacking interactions. They can associate and hydrogen bond with proteins, exhibit an intermediate size (they and/or their metabolites are likely able to cross the BBB), and have antioxidant properties; they have low toxicity, are effective BACE1 inhibitors, and demonstrate significantly higher solubility than that of curcumin. Finally, their complementary structures (rigid vs. more flexible) are relevant in nucleation/fibrillation/aggregation inhibition and/or altering the toxicity of oligomers, in the context of neurodegenerative Alzheimer's disease.

CONCLUSION

Many green chemistry candidates have been proposed for mitigating Alzheimer's disease (AD). Phenolic molecules such as flavonoids, non-flavonoids, gallotannins, elagitanins, grape seed extracts (GSE), grape juice, *etc.*, have the potential to modulate AD neuropathology and cognitive dysfunction through multiple mechanisms, including modulating oxidation and inflammation, modulating $\text{A}\beta$ metabolism, catabolism and oligomerization, and directly influencing brain activities. Moreover, experimental evidence suggests that polyphenols which target multiple disease mechanisms may have a stronger likelihood of therapeutic efficacy. De-

spite strong research and theoretical evidence, these molecules have not yielded the anticipated clinical trial results. Nevertheless, this fact should not lead researchers to entirely disregard this rich compound family, with its potential candidates for AD therapy.

Indeed, various compounds already used in manufacturing should be revisited for their anti-aggregation properties. To demonstrate these molecules' potential, we presented two tannic acid building blocks, TGG (1,3,6-tri-O-galloyl- β -D-glucose), and in greater depth, corilagin (β -1-O-galloyl-3,6-(R)-hexahydroxydiphenoyl-D-glucose). These molecules possess key characteristics and properties (hydrophobicity, aromaticity, and hydrogen bonding) important in mitigating Alzheimer's disease. They may be extracted from plants and trees through green chemistry, are of intermediate size (meaning they, and/or their metabolites, may cross the blood-brain barrier), have a hydrophobic functional character, associate quickly with protein, and their molecular complexes exhibit a colloidal behavior in terms of stability and kinetics of association. Reported to have several pharmacological activities and low toxicity, corilagin might alter the nucleation process of formation of protofibril/fibril/fiber, hence minimizing and/or altering aggregate/cluster/plaque structures. In addition, corilagin and its close analogue, TGG, may help reduce oligomer cytotoxicity.

Although we are unaware of any data in the literature on brain levels for the proposed intermediate size of natural polyphenols (*i.e.* corilagin and TGG) when administered orally to human subjects, green phenolic molecules perform well in other industries and, hence, should be further investigated as potential candidates in the fight against AD.

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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