Polyphenols as Potential Inhibitors of Amyloid Aggregation and Toxicity: Possible Significance to Alzheimer's Disease

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Abstract: Beta-amyloid (Aβ) likely plays a pivotal role in the etiology of Alzheimer's disease (AD). Consequently, Aβ–associated pathways are targets for the development of possible effective AD therapies. This review first updates strategies aimed at the inhibition of Aβ formation and then discusses the role of food-derived polyphenols as putative anti-amyloid drugs.

Key Words: Alzheimer's disease, polyphenols, neuroprotection.

INTRODUCTION

Alzheimer's disease (AD) is the most common form of dementia affecting the elderly population. The related pathogenesis remains poorly understood and many hypotheses have been raised. Although inflammation and free radicals are likely to be involved in AD pathology, the dominant hypothesis is still the "amyloid (Aß) cascade" one [1]. This hypothesis states that progressive accumulation of large intracellular and extracellular Aß aggregates play a fundamental role in neurodegeneration process seen in AD [1]. However, the "amyloid cascade" hypothesis is not fully accepted and recent studies suggest that soluble forms of Aß including dimers and small oligomers (known as Aß-derived diffusible neurotoxic ligands or ADDLs) participate in neuronal dysfunction in AD-associated neurodegeneration [2, 3]. Indeed, there is a weak correlation between fibrillar amyloid load and neurological dysfunctions observed in AD. Moreover, amyloid deposits also occur in cognitively normal individuals who have otherwise no evidence of local neuronal damage [2]. Preliminary analyses have revealed the presence of abundant soluble oligomers in AD patients, consistent with the suggestion that oligomer formation precedes plaque development and may be linked to cognitive impairments [3]. To date there is no curative treatment for AD and the existing therapies only target one of its symptoms. Based on the anti-amyloid hypothesis, it has been postulated that the modulation of Aß generation/accumulation may be a promising curative approach to stop neuronal damage associated with amyloidogenesis [4].

Hence, pre-clinical and human studies have been conducted to develop and screen for the molecules aimed to block the deleterious effects of Aß by: i) modulating the activity of the relevant producing enzymes such as secretases; ii) developing ligands capable of direct interaction with Aß thus preventing its polymerization and iii) promoting Aß clearance from the brain [4]. In parallel with anti-amyloid treatment strategies, epidemiological and pre-clinical studies suggest that diet can lower the incidence of neurological disorders [5-11]. For example, moderate consumption of red wine and regular intake of fruits, vegetables and tea have been reported to help delaying the occurrence of AD in the elderly population [5-11]. It is likely that polyphenols including flavonoids and phenolic acids that are present in high amounts in fruits, vegetables and beverages [12], contribute to the purported beneficial effects of these nutrients. In support of this hypothesis, both *in vitro* and animal studies have demonstrated the neuroprotective abilities of polyphenols in various models of toxicity induced by Aß peptides [13-24], suggesting that molecules or analogs with similar chemical structures could be considered as potential therapeutic agents [25]. In this brief review, we discuss first the various treatment strategies that have been investigated to target Aß peptides and then review current literature demonstrating the neuroprotective effects exerted by polyphenols and possible underlying mechanisms.

ANTI-AMYLOID STRATEGIES

Aβ is a 40-42 amino acid peptide with a capacity to accumulate into clusters known as amyloid plaques, one of the main hallmarks of AD [1]. This peptide sequence is a part of the transmembrane protein called the amyloid precursor protein (APP). In the amyloidogenic pathway, β-secretase cleaves APP at the border of the Aβ sequence at the extracellular side of the plasma membrane (also known as APP ectodomain) yielding a soluble APPβ (sAPPβ) form and a remaining C-terminal fragment (βCTF or C99). γ-secretase then cleaves Aβ from the N-terminal part of C99 (Fig. **1A**). In the non-amyloidogenic pathway, α-secretase cleaves APP within the Aβ sequence generating two non-amyloidogenic peptides and thus precluding Aß generation (Fig. **1B**). Intact Aβ peptides released by its cleavage from APP (*via* β- and γ-secretases) can occur in a number of conformational states ranging from monomers, dimers, small oligomers and protofibrils, to ultimately long insoluble fibrils (the main constituents of amyloid plaques) [1]. Although amyloidogenesis initiated by the activation of β- and γ-secretases has been suggested to be responsible for neuronal death in AD, the con-

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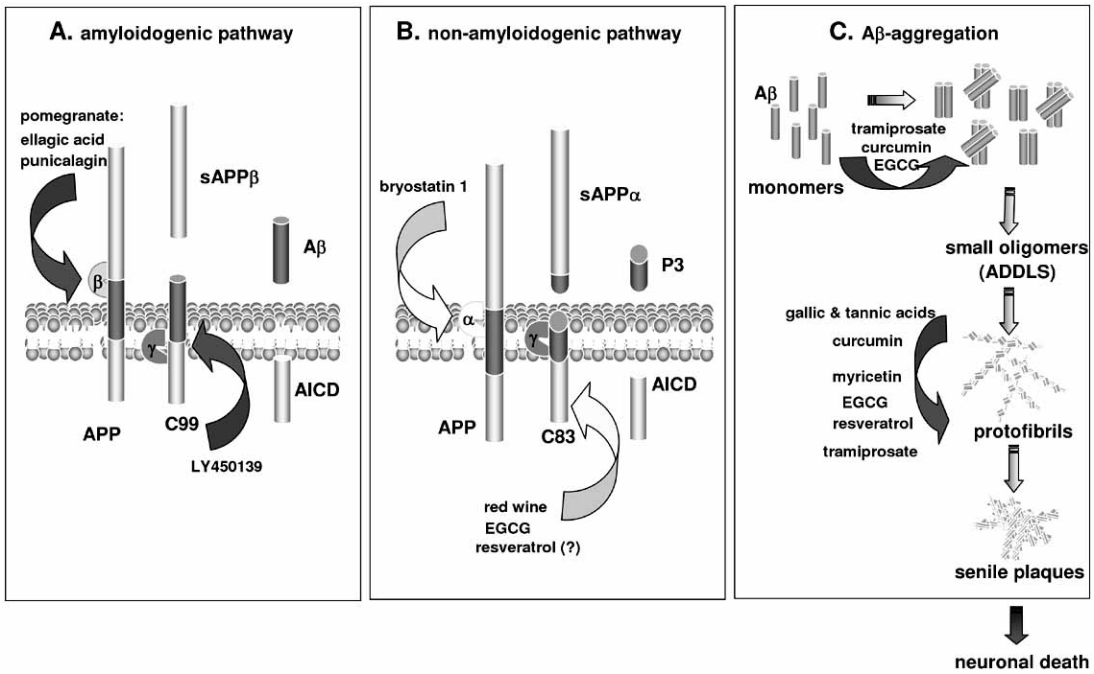

Fig. (1). Aβ biogenesis, aggregation and senile plaque formation in relation to known sites of action of compounds including polyphenols (i.e. resveratrol, myricetin, epigallocatechin gallate).

A) Amyloidogenic pathway: β-secretase cleaves APP at the extracellular side of the plasma membrane. This generates a soluble APP fragment (sAPPβ) and membrane-embedded βC-terminal fragment (βCTF or C99). Subsequent action of γ-secretase generates two soluble fragments: Aβ and AICD.

B) Non-amyloidogenic pathway: α-secretase cleaves APP inside the Aβ sequence thus precluding the biogenesis of Aβ. This leads to the formation of two fragments: a soluble APP fragment (sAPPα) and a membrane-embedded αC-terminal fragment (αCTF or C83). Subsequent action of γ-secretase generates two soluble fragments: AICD and p3.

C) Aβ aggregation: soluble, monomeric Aβ fragments aggregate into dimers and soluble small oligomers. These molecular species are also called ADDL (Aβ-derived diffusible ligands). Their further polymerization gives rise to fibrillar structures (protofibrils) and plaque deposits ("senile plaques").

Arrows indicate the known sites of actions of various compounds including polyphenols. Dark arrows indicate inhibition whereas light arrow indicates stimulation.

tribution of the various Aβ isoforms to this pathology is still a matter of debate. It has been recently postulated that the progressive accumulation of Aß aggregates is not fundamental to neurodegeneration that contributes to the progression of AD [3].

Many possible approaches have been explored to block Aß-related neurotoxicity including: i) the neutralization of plaque-, Aß protofibrils- and/or oligomers- toxicities by using vaccination or ligands; ii) the inhibition of β- and γ-secretases involved in the amyloidogenic pathway; iii) and the stimulation of α-secretase activity involved in the non-amyloidogenic pathway.

Secretase Modulation

The inhibition of β- and γ-secretase activities, leading to a reduction of neurotoxic Aβ peptides generation, is considered as one of the most promising strategies to treat AD and is being pursued by a number of pharmaceutical companies. For example, LY450139 (Lilly Research Laboratories, Indianapolis, IN, USA), a γ-secretase inhibitor (Fig. **1A**, Fig. **2**), has been shown to significantly reduce plasma (but not cerebrospinal fluid, CSF) Aβ levels in patients with AD [26]. Nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen have been reported to inhibit $Aß_{1-42}$ production *via* a mechanism that may depend on their interaction with components of the γ-secretase pathway [27]. A different strategy, involving the activation of α-secretase, has also been investigated for its therapeutic potential. It has been postulated that the activation of protein kinase C (PKC), an enzyme involved in the processing of the APP, can lead to the stimulation of α-secretase, resulting in a reduction in the production of Aβ and an increase in the putatively neuroprotective α-secretase product, sAPP (sAPPα) [28]. For example, bryostatin 1 (Fig. **2**), an activator of protein kinase C, stimulates α-secretase activity at nanomolar concentrations (Fig. **1B**), and reduces $Aß_{1-40}$ and $Aß_{1-42}$ production in a double-transgenic (APP/PS1) mouse model of AD [29]. This drug lacks of serious toxic affects (e.g. tumor promotion activity), and further large clinical trials will determine its therapeutic potential in the treatment of cognitive impairment associated with amyloidogenesis [30].

Polymerisation of Aβ

It has been hypothesized that the deposition of Aβ fibrils into Aβ plaques leads to neurodegenerative process in AD

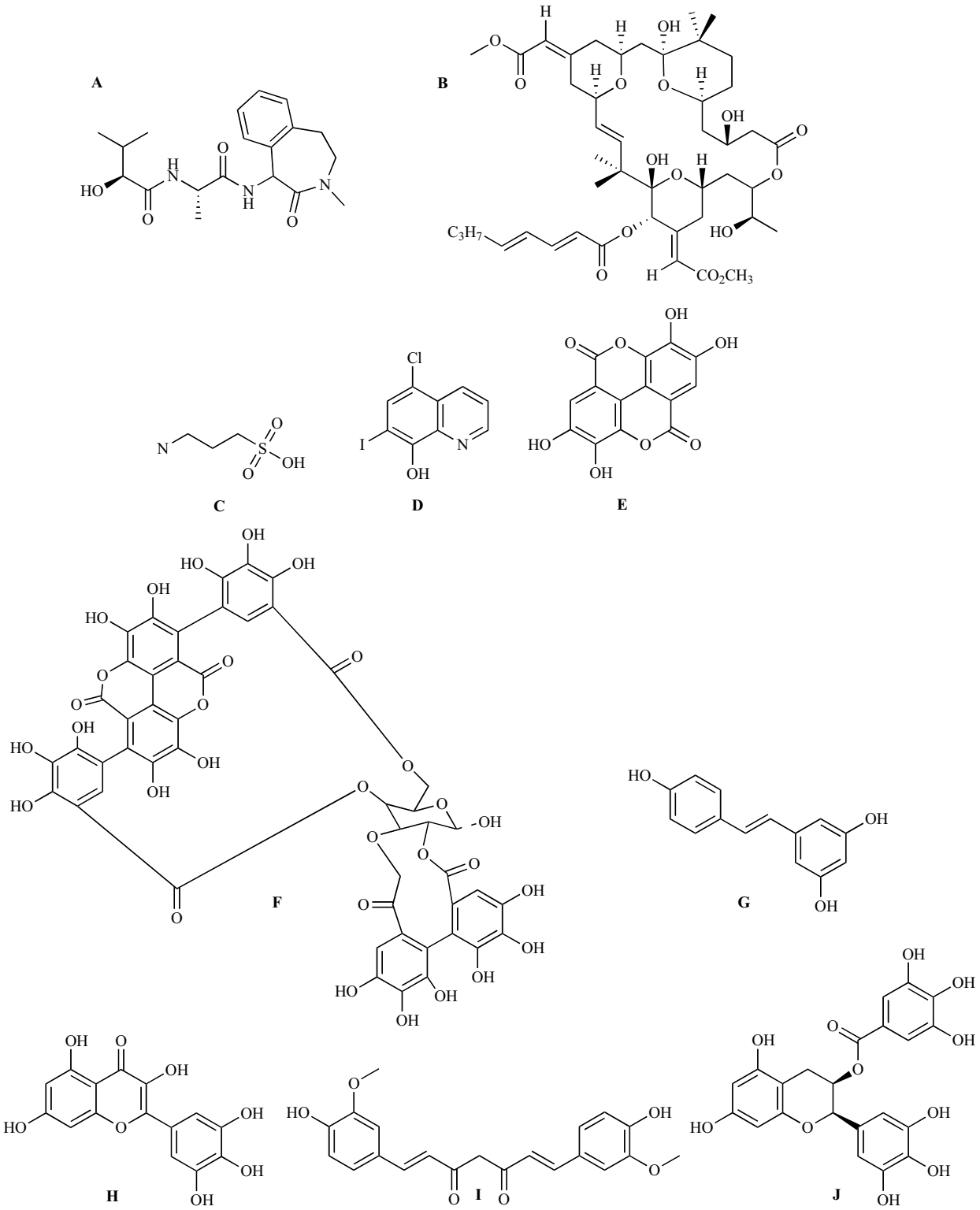

Fig. (2). Structures of compounds with purported inhibitory activities on amyloid. A) LY450139, B) bryostatin 1, C) tramiprosate, D) clioquinol, E) ellagic acid, F) punicalagin, G) resveratrol, H) myricetin, I) curcumin, and J) epigallocatechin gallate (EGCG).

and any therapy that increases clearance and/or reduces the polymerisation of Aβ may be beneficial [4]. However, recent studies suggest that soluble oligomeric Aβ is the toxic form that contributes to the pathological process [3]. Although this

issue has not been resolved yet, the prevention of Aβ formation and accumulation in the brain is an interesting target to slow the progression of AD [4]. Accordingly, tramiprosate (3-amino-1-propane-sulfonic acid, Alzhemed™, Fig. **2**) has been reported to prevent glycosaminoglycans (GAGs) from promoting the formation and deposition of Aβ fibrils and to bind to soluble Aβ [31]. A phase II clinical trial reported that tramiprosate reduced the levels of $A\beta_{1-42}$ in the CSF and seems to stabilize cognition in patients with mild to moderate AD [4]. However, the phase III clinical trial performed in North America failed to confirm the efficacy of tramiprosate in large-scale cohorts. Another phase III trial will be conduced in Europe to clearly establish if the inhibitory properties of this drug yields not only stabilization but even improvements in cognitive symptoms.

Several studies have indicated that heavy metal ions such as iron, zinc and copper may play a deleterious role in AD, suggesting that the development of therapeutic agents designed to block metal availability may be a promising therapeutic alternative for the treatment of AD [32]. Clioquinol (Fig. **2**), a copper chelator, reduced Aβ levels in brains of AD-like Tg2576 mice [33], possibly by metal-dependent upregulation of metalloprotease activity through the activation of phosphoinositol-3-kinase (PI3K) and c-jun N-terminal kinase (JNK) [34, 35]. According to the authors, these findings suggest that metal ligands including clioquinol increase cellular metal levels resulting in metalloprotease-dependent inhibition of Aβ [35]. A pilot phase II clinical trial in patients with moderate to severe forms of AD showed that clioquinol reduced plasma $A\beta_{1-42}$ levels and ameliorated cognitive status in the more severely affected group [36]. To our knowledge, the effect of clioquinol on Aβ plaques has not been investigated by the authors [36]. Based on these results, a new generation of metal ligand-based therapeutics is under development.

POLYPHENOLS AS ANTI-AMYLOID MOLECULES

Anthocyanins

A recent study reported that 6-month old transgenic mice ($Tg2576/APP_{sw}$) that feature AD-like pathologies and fed with pomegranate juice exhibited improvements in learning tasks and a reduction in Aβ plaque load in the hippocampus [37]. In this study, the authors showed that pomegranate decreased by about 50% the accumulation of soluble $A\beta_{1-42}$ and Aβ deposition as compared to control mice [37]. The beneficial effect of pomegranate on behavior and Aβ levels and deposition did not involve its capacity to alter APP processing or Aβ production, since it did not modulate either α- or ß-secretases. However, other *in vitro* studies demonstrated the inhibitory activity of two pomegranate-derived ingredients on β-secretase activity. These molecules are ellagic acid (Fig. **2**) and punicalagin (Fig. **1C**, Fig. **2**) with corresponding Ki values of 24 μM and 0.6 μM, respectively [38]. The discrepancy between *in vivo* and *in vitro* studies may be attributable to the presence of husk in the fruit extract [38].

The beneficial effects of pomegranate may be attributable to its numerous polyphenols and in particular to ellagitannins (i.e. hydrolyzable tannins), condensed tannins and anthocyanins [39, 40]. In support of this hypothesis, gallic acid and tannic acid (a polymer of gallic acid molecules and glucose) have been shown to display neuroprotective ability and to inhibit the formation of Aβ fibrils [14, 54] (Fig. **1C**). In addition, Joseph *et al*. have demonstrated that a diet enriched in blueberries (a fruit enriched in anthocyanins) reversed the deleterious effects of aging on neuronal signaling in senescent rodents and prevent cognitive deficits in APP/ PS1 transgenic mice with no alterations in Aβ deposits [41].

Moreover, Pycnogenol®, a water extract of the bark of the French maritime pine that contains high amounts of anthocyanins, protected neurons from Aβ-induced apoptosis [42] and vascular endothelial cells from Aβ-induced injury [43]. Interestingly, anthocyanins have been reported to enter the brain within minutes following intake of an anthocyanin-rich diet [44, 45].

Red Wine-Derived Polyphenols

A moderate consumption of the red wine Cabernet Sauvignon has been shown to significantly reverse cognitive impairments and attenuate $A\beta_{1-40}$ and $A\beta_{1-42}$ concentrations in Tg2576 mice [46]. This beneficial effect was accompanied by a stimulatory action on α-secretase and increase in αCTF (Fig. **1B**), suggesting that this type of red wine prevents the generation and deposition of Aβ peptides [46]. In accordance with this hypothesis, the authors found that $A\beta_{1-40}$ and $A\beta_{1-42}$ concentrations were decreased in the neocortex and hippocampus of mice exposed to red wine [46]. Some of the polyphenols found in Cabernet Sauvignon such as tannic acid, myricetin (Fig. **2**) and catechins, have been reported to possess potent anti-amyloidogenic and fibril-destabilizing effects, suggesting that these polyphenols play an important role in the neuroprotective actions of red wine. The role of resveratrol (a red-wine derived polyphenol, Fig. **2**) remains uncertain since Cabernet Sauvignon contains low amounts (0.2 mg/L) of this stilbene. However, its involvement in other cultivars such as Pinot Noir or Merlot (that have been reported to contain higher stilbene concentrations than Cabernet-Sauvignon Muscat, Concord or Grenache [47, 48]) cannot be excluded. Hence it has been shown that total resveratrol concentrations may reach 4.91 mg/L (Pinot noir) in various Japanese red wines [47] and more recently, Moreno-Labanda *et al*. showed that the average total resveratrol content, determined in a survey of 45 Spanish red wine types, was about 8 mg/L [49]. Resveratrol has been shown to display anti-amyloidogenic effect that may involve its abiliy to promote clearance, rather than to inhibit Aβ production [24]. The fact that resveratrol was not able to block Aβ production was confirmed by Marambaud *et al*. [23] who showed that resveratrol did not alter β-and γ-secretase activities. The same group also found that the ability of resveratrol to degrade Aβ may involve proteasome, a multicatalytic protease complex, but not metalloendopeptidases such as neutral endopeptidase (NEP) [23]. Finally our group reported that Aß peptides-induced cell death was dose-dependently reduced in the presence of pre- and co-treatments of resveratrol (15-40 μM) [13]. A pre-treatment with the PKC inhibitor GF 109203X significantly reduced the neuroprotective effects of resveratrol against $A\beta_{25-35}$-induced cytotoxicity, while inhibitors of MAP kinase (PD98059) and PI3 kinase (LY294002) failed to modulate the neuroprotective action of resveratrol [13]. Western blot experiments suggested that resveratrol (20-30 μM) induced the phosphorylation of PKC

Table 1. Summary of the Purported Effects of Polyphenols in Models of Toxicity Related to Amyloid Peptides

Polyphenols	Effects Obtained (Route and Duration of Administration, Model Used)	Ref.
Resveratrol	Blockade of toxicity induced by Aβ peptides	[13]
	(In vitro; 2 hr; hippocampal cells cultures)	
	Promotion of degradation of Aβ	[23]
	(In vitro; 24 hrs; cells transfected with human APP_{695})	
	Anti-amyloidogenic effect	[24]
	(In vitro; 24 hrs; hippocampal cells cultures)	Personal data
EGCG	Blockade of toxicity induced by of Aβ1-42	[14,15]
	Inhibition of Aß fibrilization AND soluble forms of Aß	
	(In vitro; 24-48 hrs; hippocampal cells cultures)	
	Decrease in Aß levels and Aß plaques	[16]
	(Ip route; 2 months; Tg APP_{sw} mice)	
	Promotion of non-amyloidogenic pathway	[17]
	Increase in levels of sAPPα secretion	
	(In vitro and oral route; 2 hrs and 7-14 days; human neuroblastoma cells and C57/BL mice)	
Gallic acid and its polymer tannic acid	Blockade of toxicity induced by Aβ peptides	[14,22]
	Inhibit of the formation of Aβ fibrils	
	Fibril-destabilizing effects	
	(In vitro; from 1 to 24 hrs; hippocampal cells cultures)	
Pomegranate (ellagic acid and punicalagin)	Improvement of behavior and AD-like pathology accompanied by reduction of soluble $Aβ_{1-42}$ and Aβ deposition.	[37]
	(Oral route; 6-8 months; Tg APPsw/Tg2576 mice)	
Myricetin	Blockade of toxicity induced by Aβ1-40	[21]
	Inhibition of the formation of Aβ fibrils	Personal data
	Fibril-destabilizing effects	
	(In vitro; from 1 to 24 hrs; hippocampal cells cultures)	
Curcumin	Reduction of amyloid levels and plaque burden	[54]
	(Oral route; 5 months; aged APPsw Tg2576 mice)	
	Inhibition of Aβ aggregation and promotion of Aβ disaggregation	[54]
	(In vitro; 3-6 days; Sections of Tg2576 mouse brain)	
	Inhibition of the formation of Aβ fibrils and fibril-destabilizing effects	
	(In vitro; from 1 to 24 hrs; hippocampal cells cultures)	[55]

and abolished the inhibitory effect of $Aß_{25–35}$ as well, thus supporting the role of PKC in the neuroprotective action of resveratrol [13].

Taken together, these *in vitro* and animal studies confirm and extend previous epidemiological studies reporting that moderate red wine consumption (two to four glasses per day) reduced by half the risk of AD and dementia [5].

Tea-Derived Catechins

Although tea is one of the most popular beverages in the world, there limited evidence that this beverage diminishes the risk of age-related neurological disorders. An epidemiological study performed in 1003 Japanese aged 70 years and older have shown that higher consumption of green, and to a lesser extent black tea, was associated with a lower prevalence (relative risks of 0.46 and 0.60, respectively) of cognitive impairments [50]. We have shown that both green and black tea extracts protected cultured hippocampal neuronal/glial cells against Aß toxicity [14]. These effects were shared by tea catechins gallate esters [i.e. epigallocatechin gallate (EGCG, Fig. **2**) and epicatechin gallate (ECG)] and gallic acid, while epicatechin (EC) and epigallocatechin (EGC) failed to protect cells. These data suggest that catechins gallate esters that are abundant in green and black teas [51] contribute to the beneficial effects of teas. Interestingly, only catechins (also called flavan-3-ol) gallate esters are able to inhibit the formation of both Aß fibrils and soluble forms

of Aß including Aß-oligomers [14]. This is in agreement with previous study showing that the most potent green tea catechin, EGCG, decreased Aß levels and plaques in Tg APP_{sw} transgenic mice, possibly through a stimulatory effect on α-secretase activity [16]. Moreover, EGCG has been found to promote non-amyloidogenic pathway *via* a PKC-dependent activation of α-secretase activity, and to increase levels of sAPPα secretion [17].

Curcumin

Curcumin (Fig. **2**) is the principal polyphenol found in the Indian curry spice that has been shown to reduce amyloid accumulation *in vivo* [52] but failed to reduce $Aß_{1-42}$ production *in vitro* [53]. Moreover, a more recent study reported that curcumin inhibited Aß aggregation with an efficacy higher than that obtained with non-steroidal anti-inflammatory drugs such as ibuprofen and naproxen, and prevented Aß oligomers formation and toxicity [53]. Moreover, *in vitro* and *in vivo* studies showed that curcumin reduced amyloid levels and plaque burden in aged Tg2576 mice with advanced amyloid accumulation [54], in agreement with its purported anti-amyloidogenic effects [55]. These data support the clinical use of low dose of curcumin for preventing or treating AD.

CONCLUSION

In summary, there is accumulating evidence suggesting that dietary intake of polyphenols play a prophylactic role to reduce the incidence of age-related neurological disorders. This is in accordance with epidemiological studies reporting an inverse correlation between the risk of AD or cognitive decline and the consumption of fruits, vegetables and beverages enriched in polyphenols [5-10]. Mechanisms of action underlying the neuroprotective measures of polyphenols are yet to be fully elucidated but likely involve their ability to counteract Aß formation/aggregation either directly by altering ß-sheet conformation (required for Aß aggregation and fibril formation) or indirectly by modulating secretases. They may also promote Aß clearance by acting on Aß degrading-enzymes such as proteasome or metallopeptidases [23]. Based on these findings and current clinical trials, we hypothesize that polyphenols or derivatives may serve as possible neuroprotective agents for the prevention of cognitive deficits. Future clinical trials will be necessary to evaluate the clinical efficacy of phenolic compounds in high-risk elderly populations.

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ABBREVIATIONS

Aβ = β-amyloid

ADDLs = Aß-derived diffusible neurotoxic ligands

AD = Alzheimer's Disease

EC = epicatechin

ECG = epicatechin gallate

EGC = epigallocatechin

EGCG = epigallocatechin gallate

GAGs = glycosaminoglycans

PKC = protein kinase C

ROS = reactive oxygen species

sAPPβ = soluble APPβ.

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