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REVIEW ARTICLE

Unveiling the Potential of Polyphenols as Anti-Amyloid Molecules in Alzheimer's Disease

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Abstract: Alzheimer's disease (AD) is a devastating neurodegenerative disease that mostly affects the elderly population. Mechanisms underlying AD pathogenesis are yet to be fully revealed, but there are several hypotheses regarding AD. Even though free radicals and inflammation are likely to be linked with AD pathogenesis, still amyloid-beta (Aβ) cascade is the dominant hypothesis. According to the Aβ hypothesis, a progressive buildup of extracellular and intracellular Aβ aggregates has a significant contribution to the AD-linked neurodegeneration process. Since Aβ plays an important role in the etiology of AD, therefore Aβ-linked pathways are mainly targeted in order to develop potential AD therapies. Accumulation of Aβ plaques in the brains of AD individuals is an important hallmark of AD. These plaques are mainly composed of Aβ (a peptide of 39-42 amino acids) aggregates produced *via* the proteolytic cleavage of the amyloid precursor protein. Numerous studies have demonstrated that various polyphenols (PPHs), including cyanidins, anthocyanins, curcumin, catechins and their gallate esters were found to markedly suppress Aβ aggregation and prevent the formation of Aβ oligomers and toxicity, which is further suggesting that these PPHs might be regarded as effective therapeutic agents for the AD treatment. This review summarizes the roles of Aβ in AD pathogenesis, the Aβ aggregation pathway, types of PPHs, and distribution of PPHs in dietary sources. Furthermore, we have predominantly focused on the potential of food-derived PPHs as putative anti-amyloid drugs.

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1. INTRODUCTION

Alzheimer's disease (AD) is one of the most devastating neurodegenerative diseases (NDs) and the most common form of dementia. Unfortunately, there are still no drugs available to cure or prevent AD. AD characteristics include extracellular plaque deposits of amyloid beta (Aβ) peptides, intracellular neurofibrillary tangles (NFTs) of misfolded and hyperphosphorylated tau protein, and the loss of synapses and neurons [1]. The amyloid cascade hypothesis is considered the most important hypothesis regarding AD pathogenesis. As per this hypothesis, Aβ deposition into plaques in brain tissues is the major causative factor of AD [2]. Aβ peptides are produced from the proteolytic cleavage of amyloid precursor protein (APP). Since Aβ is a partly folded and amphiphilic molecule, therefore Aβ is prone to self-aggregation and generates protofibrils or intermediate oligomers, and eventually insoluble fibrils [3]. Furthermore, Aβ can impair the functions of some membrane transporters, elevate cellular OS, and result in neuroinflammation, which can further lead to enormous synaptic dysfunction and loss of neurons [4]. Aβ-mediated neurotoxicity is strongly linked with the aggregated states of Aβ, where protofibrils and oligomers are

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more detrimental as compared to mature fibrils and soluble monomers. Protofibrils of Aβ and Aβ oligomers have a high capacity to interact with cell membranes, form pores, induce intraneuronal Aβ accumulation, alter membrane features, and disturb membrane receptors [5]. Nonetheless, the precise mechanisms of these processes are still not known. Therefore, it is important to find out the exact factors that mediate Aβ aggregation for AD prevention and treatment. However, many studies have already been carried out to detect and characterize intermediates that are associated with the Aβ aggregation pathway. Various techniques emphasized the isolation of Aβ aggregates from body fluids, including cerebrospinal fluid (CSF) and postmortem tissues, which were mainly purified *via* ultracentrifugation or size exclusion chromatography, and perhaps characterize the *in vivo* condition in the most dependable manner [6, 7]. Many *in vitro* studies, including structural and kinetic studies with recombinantly or synthetically expressed Aβ were carried out [8]. It was observed that stabilization of transient intermediates during *in vitro* Aβ assembly is highly challenging [9]. In Table **1**, we have summarized the Aβ species that have been identified to date.

Polyphenols (PPHs) are secondary metabolites of plants that are abundantly found in vegetables, oils, seeds, fruits, and many other foods [10]. PPHs have a number of roles, including facilitating plant reproduction and growth, imparting plant pigmentation, and protecting plants from aggression by pathogens [11]. So far, over 8000 natural PPHs have been detected. PPHs are grouped into 6 major categories according to the nature of their carbon skeletons, including flavonoids, tannins, phenolic acids and derivatives, lignans, curcuminoids, and stilbenes [12]. In ortho or para positions, all PPHs contain at least one phenolic ring bearing one or more hydroxyl groups [13]. PPHs act as strong antioxidants because of their ability to chelate redox-active metal ions, including iron [14] and to scavenge free radicals produced *via* reactive oxygen species (ROS) [15]. Collectively, these properties indicate a protective effect of PPHs against oxidative stress (OS) [16]. Dietary intake of PPHs is markedly higher than other dietary antioxidants, such as- carotenoids, vitamin C, and vitamin E [17, 18]. Additionally, PPHs also show anti-inflammatory properties [19]. It has been demonstrated that PPHs exert various beneficial effects in preventing various OS-linked diseases, including NDs, inflammation, atherosclerosis, and cancer [20-23].

The modulating or suppressive activities on Aβ aggregation have already been observed in 44 PPHs [24]. In a study, Ono *et al.* [25] revealed that wine-associated phenols, including (-)-epicatechin, (+)-catechin, kaempferol, quercetin, morin, and myricetin destabilized preformed Aβ fibrils and suppressed the generation of Aβ fibrils from Aβ40 and Aβ42 in a dose-dependent manner. In addition, similar effects were also achieved with resveratrol, olive tree-derived PPHs, epigallocatechin gallate (EGCG), tannic acids, rosmarinic acid, curcumin, and other stilbenes [26-30]. It has been reported by *in vivo* studies that several PPHs, including curcumin, resveratrol, and EGCG, reduced Aβ levels and their plaque formations in the brains of mouse models [31-33]. Indeed, the capacity of PPHs to avert the polymerizations of Aβ was found to be facilitated *via* their binding with ions or *via* direct interaction with Aβ, which further mediates Aβ aggregations [24]. In this review, we have summarized the effects of Aβ in the pathogenesis of AD, the Aβ aggregation pathway, types of PPHs, and distribution of PPHs in dietary sources. Moreover, we have particularly focused on the potential of PPHs as anti-amyloid molecules.

Table 1. Amyloid beta (Aβ) species and their characteristics.

Aβ Species	Properties	Study Models	Refs.
Amyloid fibrils	Stable and filamentous Aβ aggregates with fibrillar structure and common structural features	*In vitro*; patients with AD; mouse models	[34-36]
Aβ protofibrils	Flexible, short, rod-like structure; <200 nm in length; 6-8 nm in diameter; toxic; precursor of mature fibrils	*In vitro*	[37-40]
Aβ Plaques	Mainly composed of fibrils; not toxic; large extracellular Aβ deposits; surrounded by reactive astrocytes, activated microglia, axons, and dystrophic dendrites	*In vivo*; patients with AD; mouse models	[41, 42]
Aβ derived diffusible ligands (ADDLs)	Neurotoxic; nonfibrillar; an estimated mass of 17-42 kDa; trimers to 24 mers	*In vitro*; brain extracts of humans and murine models	[43, 44]
Small oligomers	Toxic; mostly unstable and transient; comprised of 3-50 monomers; heteromorphous	*In vivo*; AD individuals; mouse models	[6, 9, 45-48]
Annular Aβ oligomers	Play significant roles in membrane-disrupting ion channels or pores	*In vitro*; cell culture	[49-53]
Aβ Monomers	Mainly α-helical and random coil in structure; produced from APP; soluble amphipathic molecule	*In vitro*; *in vivo*; human brain extracts	[54-56]
Aβ Dimers	Diameter of around 35 nm; hydrophobic core	*In vitro*; *in vivo*; human brain extracts	[57-59]
Aβ Trimers	Act as a subunit of toxic oligomers	*In vivo*; mouse models	[6, 60]

2. ROLES OF Aβ IN THE PATHOGENESIS OF ALZHEIMER'S DISEASE

AD is fatal progressive dementia and its characteristics include extracellular accumulation of Aβ plaques and intracellular NFTs in human brain tissues [61, 62]. Aβ peptides mainly make up the extracellular deposits, whereas hyperphosphorylated tau proteins make up the NFTs [36]. Aβ peptide is a normal product of the cellular metabolism derived from the APP [63]. Aβ peptides that are composed of 39-42 amino acids are sequentially cleaved from the APP's C-terminal region [63], along with various isoforms that are generated *via* alternative splicing [64-66]. As per the amyloid hypothesis, aggregation of Aβ peptides is the cause instead of an AD effect [67]. There are several facts that strongly favor the amyloid hypothesis, including elevated *in vitro* aggregation tendency of familial AD (FAD)-linked Aβ variants, the link of amino acid substitutions in Aβ with early-onset FAD, the colocalization of Aβ aggregates along with dying neurons, and the production of an AD phenotype in transgenic mouse models overproducing Aβ or overexpressing APP *via* enhanced APP cleavage [68-71]. AD is linked with a rise in the $A\beta_{1-40}/A\beta_{1-42}$ ratio. Although the abundance of $A\beta_{1-40}$ is 10 times more than that of $A\beta_{1-42}$, but it has been observed that $A\beta_{1-42}$ is the predominant toxic and/or amyloidogenic species [71-75]. Indeed, Aβ aggregation takes place before the generation of NFTs [76]. Furthermore, in contrast with deposits of Aβ peptides, NFTs are not inevitably present in the brain tissues of AD individuals [76]. Moreover, inherited mutations in tau proteins can result in frontotemporal dementia with parkinsonism, instead of inducing AD [77, 78].

Aβ exerts various neurotoxic effects, including OS, the generation of ion channels and membrane disruptions, employment of various cellular factors, or activation of multiple cellular mechanisms, including inflammation and apoptosis [79-81]. Although attention was initially paid to Aβ fibrils, however growing evidence over the past years indicated that lower-order Aβ oligomers mainly exert neurotoxic effects [82, 83]. In the brains of AD individuals and mouse models, AD symptoms, including cognitive dysfunction, memory impairment, and synaptic loss, are better correlated with the levels of soluble Aβ oligomers as compared to the presence of insoluble Aβ plaques [84-86]. In addition to this, initial symptoms of AD might even take place before the accumulation of Aβ plaques [87]. An increased level of lower-order and soluble Aβ oligomers has been detected in human AD brain tissues [88, 89]. It was also observed that the generation of soluble Aβ oligomers takes place before AD development [90]. Oligomeric species derived from cell cultures and murine AD brains showed toxic effects [69, 91]. Owing to the extracellular location of Aβ plaques, it is assumed that toxic effects can occur from the extracellular attack of neurons *via* Aβ [69, 91]. Nonetheless, Aβ also exists intracellularly in rat brain tissues and cell cultures [92, 93]. It has been demonstrated that nonfibrillar and intracellular Aβ oligomers can exert strong cytotoxic effects and can even exceed extracellular Aβ species [94, 95].

3. THE PATHWAY OF Aβ AGGREGATION

It is a very complex task to elucidate the Aβ aggregation pathway [96, 97]. The Aβ fibrillization model is mediated by a nucleation-dependent polymerization process that necessitates seeding *via* an ordered nucleus. Subsequently, the growth of the oligomers occurs through the incorporation of Aβ. Indeed, in this model, nuclei formation with seeding function is considered as the rate-limiting step. This observation is in line with the detected lag phase in the generation of Aβ fibrils that can be removed *via* adding preformed seeds [37, 98-100]. Aβ seeding is very specific, while seeds derived from other amyloidogenic proteins cannot effectively induce Aβ fibrillization [101]. Furthermore, Aβ fibril formation needs a minimum Aβ concentration. This required concentration is between 10 and 40 μM for the fibrillization of $A\beta_{1-40}$ and approximately 5-times lower for $A\beta_{1-42}$. Aβ concentration was found to be inversely proportional to the time Aβ stays soluble *in vitro* [102]. Seeding does not induce Aβ fibril generation and non-specific aggregation of Aβ becomes dominant at 50 times supersaturated Aβ levels, which surpass the physiological Aβ level around 10,000 times [103]. Interestingly, at around 10-fold lower concentrations, $A\beta_{1-40}$ and $A\beta_{1-39}$ remained soluble for several days, while $A\beta_{1-42}$ rapidly aggregated into fibrils [104-106]. Collectively, these findings suggest that a minimum concentration of Aβ is needed for ordered aggregation, whereas a maximum Aβ concentration occurs above which non-specific Aβ aggregation averts certain Aβ polymerization [107].

It has been observed that the aggregation mechanisms for the same Aβ might differ at different initial Aβ levels [108-110]. It has also been confirmed that $A\beta_{1-40}$ and $A\beta_{1-42}$ aggregation occur through different mechanisms [9, 54]. In general, the common characteristics of the concluded assembly models involve Aβ oligomer formation as a nucleus which is considerably smaller as compared to Aβ fibrils. In addition, the *in vivo* nuclei growth mediated by fibrils and protofibrils ultimately bind with plaques, which eventually results in the generation of off-pathway intermediates [37, 111, 112] (Fig. **1**). Studies on full-length, C- and N-terminally truncated Aβ suggest that Aβ residues 17-21 and structural alterations in this Aβ segment are important for the early phases of assembly [113, 114]. Models for the transition of monomer-to-oligomer also exist. Aβ monomers occur in equilibrium between the β-sheet and α-helical conformations, wherein solely the β-sheet structure exists in self-assembly-competent form and is pulled from the equilibrium. The monomer conformation is essential for fibrillization, which is induced by the formation of β-turn in the Aβ segment 24-28 [54]. Studies involving high-resolution atomic force microscopy indicated the generation of Aβ octamers, tetramers, and dimers containing β-sheet conformation as early assembly intermediates [115].

Another model is based on the evidence that α-helix-rich oligomeric intermediates accumulate in case of fibrillization [116]. In addition, the shift to a β-sheet may therefore take place at the oligomer levels, as low-molecular-weight and soluble oligomers contain α-helical structure, while insoluble and higher-order only exhibit β-sheet conformation [117-119]. Fibril formation from protofibrils might be entropically driven *via* hydrophobic contacts between three and six protofibrils that are assumed to form a fibril [120]. It has been indicated by real-time monitoring of fibril growth that the reaction is a cooperative process with a constant elongation

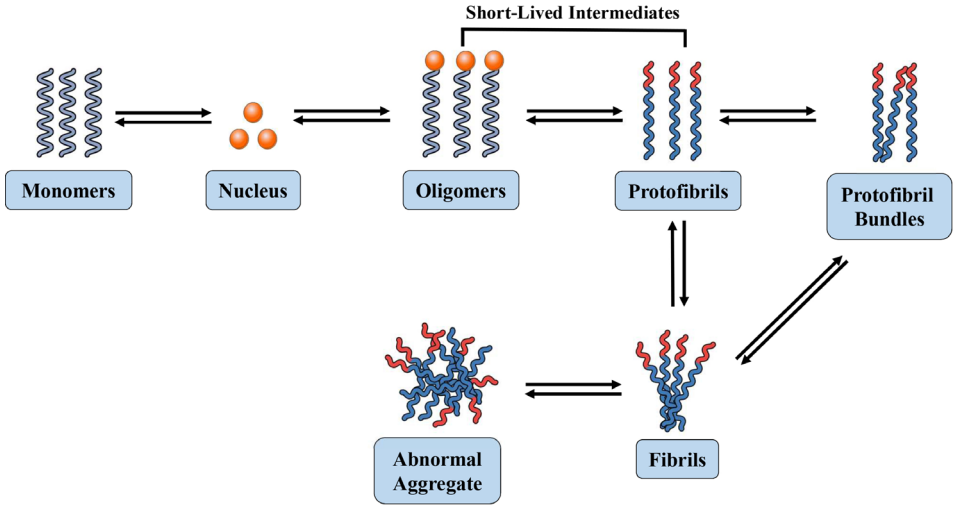

Fig. (1). Schematic representation of Aβ fibrillization process. (*A higher resolution/colour version of this figure is available in the electronic copy of the article*).

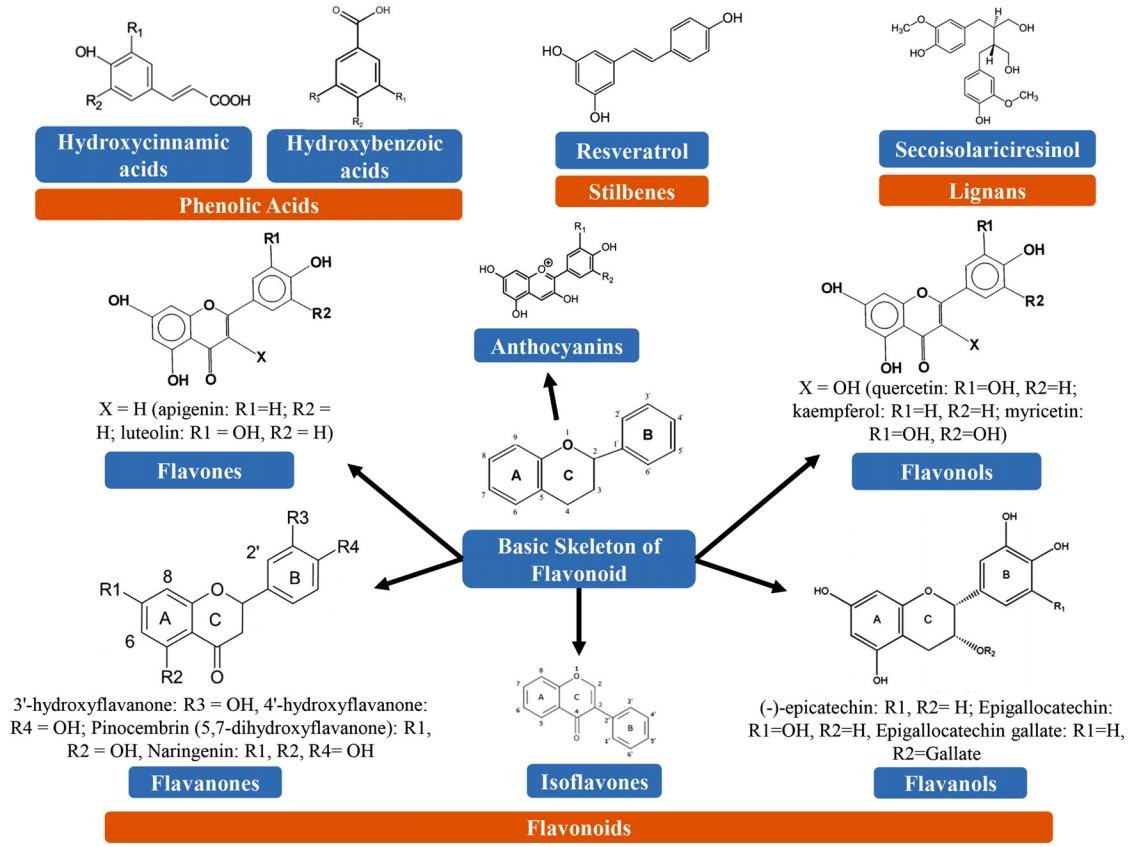

Fig. (2). Chemical structures of various types of polyphenols.

rate [121]. Molecular recycling also occurs in fibrils, wherein Aβ can get dissociated from the end of a fibril and get reassociated with another fibril [122]. These results indicate that fibril formation is a reversible process. On the other hand, real equilibria between soluble Aβ monomers and fibrils only occur at the fibril end. It has been estimated that an equilibrium concentration for the soluble $A\beta_{1\text{-}40}$ monomer is 0.7-1.0 μM, which is not dependent on the total $A\beta_{1\text{-}40}$ concentration in fibrillization processes [111]. In healthy people, Aβ is generated intracellularly and then secreted into the extracellular spaces. Aβ is usually produced in endocytic vesicles, which has been identified in the Golgi apparatus, endoplasmic reticulum, as well as at the plasma membrane and in recycling endosomes [123-125]. *In vivo* seeding has been detected in marmosets following inoculation with brain tissues derived from an individual with FAD [126]. Furthermore, the intracellular presence of Aβ aggregates in human brain tissues and cultured neurons has also been observed [127]. However, intracellular Aβ aggregates were not detected in late AD stages [128, 129].

4. TYPES OF POLYPHENOLS

Over 8000 plant-derived polyphenolic compounds have already been detected. There is a close precursor (shikimic acid) or a common intermediate (phenylalanine) in the case of all plant-derived phenolic compounds. They are mainly found in conjugated forms, along with one or more sugar residues attached to hydroxyl groups, even though direct linkages of the sugar (monosaccharide or polysaccharide) to an aromatic carbon also occur. Links with other compounds, including lipids, amines, organic acids, and connections with other phenols, have also been observed [130]. PPHs could be categorized into different groups on the basis of the number of phenol rings that they possess and based on the structural elements that bind these rings to one another. The major classes of PPHs include flavonoids, phenolic acids, lignans, and stilbenes [131]. Chemical structures of different types of PPHs are illustrated in Fig. (**2**). In Table **2**, we have summarized the class and subclasses of PPHs.

Table 2. Classification of polyphenols.

Class	Subclass	Polyphenolic Compounds	Refs.
Phenolic Acids	Hydroxycinnamic acids	Rosmarinic acid, caffeoylquinic acid, sinapic acid, ferulic acid, caffeic acid, and p-coumaric acid	[132-135]
	Hydroxybenzoic acids	Ellagic acid and gallic acid	[136, 137]
Flavonoids	Flavanols	Epicatechin, epigallocatechin, epicatechin, and catechins	[138, 139]
	Anthocyanidins	Cyanidin, malvidin, petunidin, peonidin, delphinidin, and pelargonidin	[140-142]
	Flavanones	Eriodictyol, hesperidin, hesperetin, and naringenin	[143, 144]
	Isoflavones	Genistein and daidzein	[145-147]
	Flavones	Luteolin and apigenin	[148]
	Flavonols	Rutin, kaempferol, and quercetin	[149-151]
Stilbenes	Stilbenes	e-Viniferin, piceatannol, and resveratrol	[152, 153]
Lignans	Lignans	Matairesinol, lariciresinol, pinoresinol, secoisolariciresinol, enterolactone, enterodiol, arctigenin, and sesamin	[154, 155]
Other polyphenols	Curcuminoids	Curcumin	[156]
	Hydroxyphenylpropnes	6-Gingerol	[157]

4.1. Phenolic Acids

Phenolic acids are most commonly found in foods. Furthermore, they can be grouped into two types, including cinnamic acid derivatives and benzoic acid derivatives. However, the level of hydroxybenzoic acids is usually low in edible plants, along with the exception of certain onions, black radish, and red fruits, which can possess concentrations of several tens of milligrams per kg in fresh weight [12]. As compared to hydroxybenzoic acids, hydroxycinnamic acids are more abundant and composed mainly of sinapic, ferulic, caffeic, and *p*-coumaric acids.

4.2. Flavonoids

Flavonoids are the most extensively studied type of PPHs. Flavonoids possess a common basic structure containing 2 aromatic rings attached with 3 carbon atoms that produce an oxygenated heterocycle (Fig. **2**). So far, over 4000 flavonoids have been detected and most of them are accountable for imparting attractive colors to the leaves, fruits, and flowers [158, 159]. On the basis of the different types of heterocycles involved, flavonoids can be divided into 6 major subclasses, including isoflavones, anthocyanins (ANTs), flavanols, flavanones, flavones, and flavonols. Individual differences within each group can emerge from their level of alkylation and/or glycosylation and their variation in the arrangement and number of the hydroxyl groups [131]. Some of the most common flavonoids include catechins, myricetin, and quercetin.

4.3. Stilbenes

Stilbenes are phenolic compounds and their 2 phenyl moieties are linked through a two-carbon methylene bridge. These phenolic compounds are less commonly found in the human diet. In plants, most stilbenes play a role as antifungal phytoalexins, where these compounds are generated following the pathogenic attack. Resveratrol (3,5,4′-trihydroxy-trans-stilbene) is one of the most prominent PPHs which is widely found in grapes [160].

4.4. Lignans

Lignans are diphenolic compounds that have a 2,3-dibenzylbutane structure. Furthermore, these diphenolic compounds are generated *via* the dimerization of 2 cinnamic acid residues (Fig. **2**). Various lignans, including secoisolariciresinol, are regarded as phytoestrogens. Linseed is one of the richest dietary sources of plant lignans, which has low quantities of matairesinol and secoisolariciresinol (up to 3.7 g/kg dry weight) [161].

5. DISTRIBUTION OF POLYPHENOLS IN DIETARY SOURCES

In plants, the distribution of phenolics at the subcellular, cellular, and tissue levels can vary. Soluble phenolics are found in cell vacuoles, whereas insoluble phenolics are found within the plant cell walls [162]. Various PPHs, including quercetin, are present in all plant products, such as

tea, fruit juices, cereals, vegetables, and fruits, while isoflavones and flavanones are limited to certain foods [163, 164]. Complex mixtures of PPHs are present in various dietary sources. It has been observed that an increased level of phenolics is found in their outer parts as compared to those found in their inner layers [165]. There are many factors that can affect the polyphenolic contents of plants, including environmental factors, storage, processing, and the extent of ripeness during the time of harvest. Environmental factors and edaphic factors, including rainfall, sun exposure, and soil type, can also greatly affect the polyphenolic content of the foods. Indeed, the extent of ripeness can significantly affect the proportions and levels of several PPHs [166]. An increased level of anthocyanin and a decreased level of phenolic acid have been reported during ripening. Numerous PPHs, including phenolic acids, are directly linked with the reaction of plants to various types of stress. For instance, PPHs play a role in healing *via* lignifications of injured regions and possess antimicrobial *via* elevating their levels following pathogenic attack [165, 167, 168].

Storage also directly affects the polyphenolic contents of the foods. It has been confirmed that the polyphenol content of the foods can alter due to storage, owing to the easy oxidation of these PPHs [166]. Furthermore, oxidation reactions can further lead to the generation of polymerized substances, which can further result in alterations in the quality of foods, specifically in terms of organoleptic characteristics and color. Such alterations might be beneficial in the case of black tea, whereas they can be detrimental in the case of fruit browning. Interestingly, storing wheat flour could lead to a significant loss of phenolic acids [169]. It was also observed that when flour was stored for 6 months, qualitatively, it possessed the same phenolic acids, however, their concentrations were decreased by 70% than fresh flour. In contrast, cold storage has a minor effect on the level of PPHs in onions, pears, or apples [169]. Moreover, cooking has a significant effect on the concentration of PPHs. Tomatoes and onions lose around 75% to 80%, 65%, and 30% of their initial content of quercetin after boiling (for 15 minutes), microwave oven cooking, and frying, respectively [170].

6. POLYPHENOLS AS ANTI-AMYLOID MOLECULES

6.1. Anthocyanins

Along with other PPHs, a high level of ANTs is present in pomegranate juice [171]. In a study, supplementation with pomegranate juice resulted in enhanced task learning and decreased the load of Aβ plaque in the hippocampus of transgenic mouse models (Tg2576/APPsw) [172]. Furthermore, in this study, the researchers revealed that pomegranate reduced the Aβ deposition and soluble Aβ1-42 accumulation by around 50% more than that of control mouse models [172]. Several *in vitro* studies have also confirmed the suppressive property of 2 pomegranate-derived molecules, including punicalagin and ellagic acid (Fig. **3**), on β-secretase activity [38]. The beneficial activities of pomegranate might be responsible for its many PPHs, particularly ANTs, condensed tannins, and ellagitannins (*i.e*., hydrolyzable tannins) [173]. Tannic acid and gallic acid suppressed the Aβ fibril formations and showed neuroprotective properties [174, 175]. In a study, Joseph *et al.* [176] showed that supplementation with blueberries (a fruit that contains a high level of ANTs) prevented cognitive impairments in APP/PS1 transgenic mouse models along with no changes in Aβ deposits and reversed the harmful effects of aging on neuronal signaling pathways in senescence-accelerated rodents [176]. Pycnogenol® (PYC) (a French maritime pine bark extract) contains a high concentration of ANTs and this compound provided protection to vascular endothelial cells against Aβ-induced damage and neurons against Aβ-mediated apoptosis [177, 178]. Moreover, in a dose-dependent manner, PYC treatment (10-60 μg/ml) before the exposure of $A\beta_{25-35}$ markedly reduced the proportion of apoptotic cells. On the other hand, PYC administration at the dose of 40-μg/ml reduced the proportion of apoptotic cells by 80% [177]. It has also been reported that following consumption of an anthocyanin-rich diet, anthocyanin has the ability to enter the brain within minutes [179, 180].

Multiple studies have indicated that berries that contain higher levels of ANTs, cyanidins and their glycosides have the ability to suppress the formation of amyloid filaments [181, 182]. Therefore, it is important to identify potent antioxidants that have the capacity to provide protection to astrocytes and brain tissues against OS. Date-palm fruit contains increased levels of ANTs, dietary fiber, and phenolic acids (including caffeic acid, protocatechuic acid, and ferulic acid). Tg2576 mouse models (that received diet rich in date palm fruits) showed a markedly lower level of Aβ as compared to the Tg2576 mouse models without the diet supplement. In AD mouse models, neuroprotective property showed by 4% date palm fruits is greater than 2% date palm fruits [183]. Supplementation with date fruits also resulted in a decreased Aβ level in rats suffering from severe anxiety behavior and AD, which further lowered AD risk [184]. Several berries contain potent ANTs that may provide protection against AD *via* various mechanisms [181, 185]. In this regard, for example, ANTs present in green tea and red raspberry are useful in reversing the AD effects [186, 187]. Intake of bilberries caused a marked decrease in the levels of soluble Aβ40 and Aβ42 in transgenic AD mouse models, as compared to the mouse models fed with blackcurrant. Administration of bilberry and blackcurrant extracts decreased APP levels in the cerebral cortex of AD mice, however, alterations in the tau phosphorylation and expression were not seen [188].

ANTs can penetrate the blood-brain barrier and provide protection to brain tissues against OS-induced apoptosis, mitochondrial dysfunction, and Aβ toxicity [189]. Interestingly, a formulation containing ANTs/anthocyanidins reduced $A\beta_{1-42}$-induced tau-phosphorylation [187]. In a study, Isaak *et al.* [190] showed that lingonberry ANTs (cyanidin-3-arabinoside, cyanidin-3-glucoside, and cyanidin-3-galactoside) protected the cells from hydrogen-peroxide-mediated apoptosis in H9c2 cells at the concentration of 10 ng/mL (20 nmol/L). In a different study, Badshah *et al.* [191] reported that neurodegeneration induced by $A\beta_{1-42}$ in case of AD might be reversed *via* using potent antioxidants, such as black soybean ANTs. In addition, AD could be reversed *via* ANTs by the mitochondrial apoptotic pathway by controlling BACE-1, tau, caspase-3, caspase-9, cytochrome c, and Bax [191, 192]. Pacheco *et al.* [193] and Gutierres *et al.* [194] estimated the

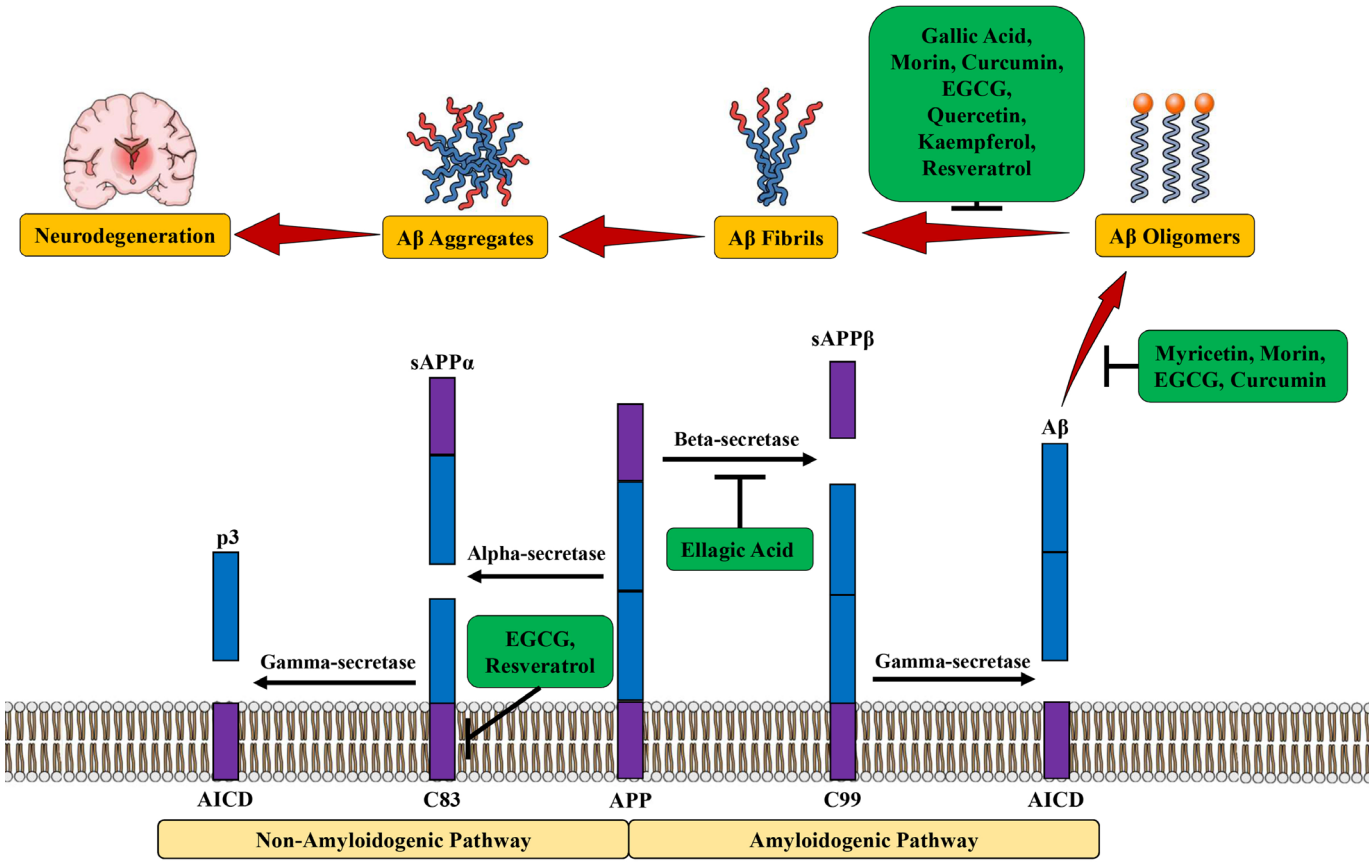

Fig. (3). Anti-amyloid potential of various polyphenols. **Abbreviations**: AICD, amyloid precursor protein intracellular domain; APP, amyloid precursor protein; Aβ, amyloid beta; EGCG, epigallocatechin gallate; sAPPα, soluble APPα; sAPPβ, soluble APPβ. (*A higher resolution/colour version of this figure is available in the electronic copy of the article*).

levels of acetylcholinesterase (AChE), Ca^{2+} ATPase, *Na^+/K^+-ATPase*, and nitrite/nitrate functions in the hippocampus and cerebral cortex of an AD mouse model. These researchers also revealed that ANTs can regulate cholinergic neurotransmission and ion pump activity, which can further lead to enhanced memory. ANTs derived from black chokeberry protected the SH-SY5Y cells from $A\beta_{1\text{-}42}$-induced apoptosis *via* controlling calcium homeostasis. These ANTs also reduced ROS and intracellular calcium levels, however, they caused elevated mitochondrial potential and ATP.

The aglycone forms of ANTs, including malvidin and malvidin-3-glucoside preserved calcium homeostasis, and showed protective properties against neurotoxicity induced by $A\beta_{1\text{-}40}$ and $A\beta_{25\text{-}35}$, and improved neurological dysfunction [195]. Grapes also serve as a very rich source of ANTs [186, 196]. Grape seeds also serve as a rich source of pro-ANTs, which protect from DNA fragmentation, OS, and lipid peroxidation. It has been observed that grape seeds obtained from nine grapevines (*Vitis vinifera* L.) varieties are found to possess 22 distinct ANTs, where the ANT levels vary between 0.5 and 4.99 g/kg. The concentration and type of ANTs depend on the cultivation season and variety. Grapes also contain several major aglycone forms of ANTs, including malvidin, peonidin, and delphinidin [186, 197]. There is a growing use of berries in health products owing to the claim that berries can provide protection against several diseases and promote mental health [187, 198]. Furthermore, the nutrients that are present in berries may even slow down AD progression [199]. AD progression and mitochondrial dysfunction may be subdued *via* ANTs because of their capacity to decrease intracellular calcium levels, Aβ-induced apoptosis, and ROS. In addition to this, ANTs can increase mitochondrial membrane potential and ATP levels. Collectively, these findings suggest that ANTs have the potential to suppress ROS and AD [200].

6.2. Curcumin

Curcumin (a major PPH and turmeric component) decreased *in vivo* Aβ accumulation (Table **3**) [201], however, this PPH failed to decrease *in vitro* Aβ1-42 generation [202]. Curcumin also significantly suppressed Aβ aggregation and averted the formation of Aβ oligomers and toxicity [202]. Curcumin was found to suppress the level of disaggregated fibrillar Aβ40 (IC_{50} = 1 μm) and aggregation (IC_{50} = 0.8 μm). As compared to naproxen and ibuprofen, curcumin significantly suppressed the level of Aβ40 aggregation, and averted the formation of Aβ42 oligomers and toxicity between 0.1 and 1.0 μm [175]. Furthermore, it has been revealed by *in vivo* and *in vitro* studies that curcumin decreased the amyloid plaque burden and amyloid concentrations in aged Tg2576 mouse models with progressive Aβ accumulation [175]. Collectively, these findings suggest the

clinical use of a low dose of curcumin to treat or even prevent AD. Curcumin also decreased *in vitro* Aβ concentrations *via* decreasing the expression of beta-secretase 1 (BACE1) and the maturation of APP [203]. Demethoxycurcumin showed potent inhibitory BACE-1 function (IC_{50} = 17 μM) *in vivo in* a drosophila AD model*, which further rescued* behavioral and morphological impairments induced *via* overexpression of BACE1 and APP maturation [204]. Curcumin also suppressed the transcription of BACE-1 *via* activation of Wnt/β-catenin signaling [205, 206]. It has also been suggested that curcumin can bind with Aβ and prevent *in vitro* and *in vivo* Aβ aggregation. Curcumin showed a higher affinity for binding with Aβ aggregates (*K*d = 0.20 nM), where EC_{50} of curcumin for the destabilization of Aβ was around 1 μM [28]. In a study, Garcia-Alloza *et al.* [207] reported that intravenous administration of curcumin at the dose of 7.5 mg/kg for 7 days cleared or decreased the size of Aβ plaques in APPswe/PS1dE9 mouse models. Oral administration of a daily single-dose (500 ppm) of curcumin for 5 months markedly decreased the concentrations of Aβ plaques (by 32.50%) and insoluble Aβ (by 85%) [208].

Comprehensive structure-activity relationship studies have revealed that substitution conformation of the phenol rings, rigidity and length of the linker, and coplanarity of two phenol rings influence the inhibitory potential of curcumin [209]. By utilizing molecular dynamics simulations and molecular docking, Rao *et al.* [210] confirmed that binding of curcumin with Aβ aggregates can result in considerable amino acid variations and cause a shift in equilibrium towards non-toxic Aβ aggregates. Curcumin also has the ability to bind strongly with Aβ *via* hydrogen bond and hydrophobic interactions, which can further lead to the prevention of oligomerization and disruption of preformed fibrils [211]. Furthermore, curcumin can block Aβ aggregation *via* chelating various metal ions, including Fe^{3+}, Cu^{2+}, and Zn^{2+}, that are responsible for inducing OS and Aβ aggregation [212, 213]. In a study, Kozmon [214] revealed that curcumin has the capacity to chelate Cu^{2+} ions and directly bind with Aβ, which further results in curcumin-Aβ and curcumin-Cu^{2+}-Aβ complexes that eventually reduce toxic β-sheet structure [214]. Along with the activities of curcumin to regulate Aβ aggregation and generation, it also induces Aβ clearance. Moreover, curcumin increased expressions of lysosome- and autophagy-linked protein markers including beclin-1, LC3A/B-II, and heat shock proteins, which are crucial for the phagocytosis of Aβ peptides in neurons [215]. CNB-001 is a derivative of curcumin that acts as an inhibitor of 5-lipoxygenase. CNB-001 activates PERK-eIF2-ATF4 of the unfolded protein response (UPR) and induces Aβ degradation [216]. Collectively, these findings suggest that curcumin not only regulates the Aβ cascade but also plays an important role in identifying various novel targets for AD treatment, including PERK-eIF2-ATF4 of the UPR and Wnt/β-catenin pathway.

6.3. Tea-Derived Catechins

In an epidemiological study, it was reported that increased green tea consumption (and, to a lesser degree, black tea consumption) was linked with a lower level of cognitive deficits in 1003 Japanese people aged 70 [217]. Extracts of black and green teas also provided protection to hippocampal glial/neuronal cells against Aβ toxicity [14]. In addition, these activities were also observed with gallic acid, epicatechin gallate, and epigallocatechin gallate (EGCG), whereas epigallocatechin and epicatechin could not provide protection to cells. Catechins gallate esters that are most commonly found in black and green teas play a role in the beneficial properties of teas [218]. Catechins and their gallate esters have the capacity to suppress the generation of Aβ fibrils and Aβ's soluble forms, including Aβ-oligomers. EGCG reduced Aβ plaques and levels in Tg APPsw transgenic mouse models [219]. Numerous *in vitro, in vivo,* and *in silico* studies have been carried out to assess the effects of catechins in AD [220-223]. Since catechins possess antioxidant properties, therefore they might provide protection against OS-linked neurodegeneration in the case of late-onset NDs [224, 225]. It is well known that levels of oxidized DNA, proteins, and peroxidized lipids are elevated in AD individuals [226]. In a study, Haque *et al.* [227] observed that the administration of catechins that occur in green tea averted Aβ-induced cognitive deficits in rat models [227]. In addition to this, both plasma and hippocampal ROS and lipid peroxide levels were decreased by 20% as compared to controls, which indicates a marked reduction [227].

In another study, Biasibetti *et al.* [228] assessed the activities of EGCG in streptozotocin-induced dementia rat models. It was revealed by the Morris water maze test that oral administration of EGCG at the dose of 10 mg/kg/day for a month reversed cognitive deficits, decreased nitric oxide (NO) generation, and reduced the levels of ROS [228]. Metal iron-chelating and free radical scavenging properties of catechins might play roles in these antioxidant effects [229-231]. Various metal ions, including iron (III) and copper (II), could be chelated *via* catechins. Furthermore, iron chelation decreases ROS generation by suppressing the Fenton reaction [232]. It has already been observed that iron (III) and copper (II) can accumulate in the brains of AD individuals [233]. Collectively, these results indicate that tea catechins have the capacity to decrease OS in the brain and peripheral tissues. Furthermore, they also can inhibit behavioral changes linked with cognitive impairment. Catechins exert anti-inflammatory activities, which might also indicate the mechanism of their activities on AD. It has been observed that neuronal injury can result in the release of various pro-inflammatory elements, including cytotoxic elements and cytokines, which can eventually result in neuronal death [234]. In lipopolysaccharide (LPS)-injected mouse models, Lee *et al.* [235] confirmed that EGCG preadministration at the doses of 1.5 and 3 mg/kg for 3 weeks averted LPS-mediated memory deficits and inhibited the rise of inflammatory proteins and cytokines observed in nontreated controls [235].

In a study with BV-2 microglia, EGCG suppressed the reactions linked with LPS-induced inflammation, such as expressions of inducible NO synthase, NO generation, and cyclooxygenase-2 expressions [236]. PKC-linked processes might also play roles in the activities of catechins in AD. Moreover, PKC plays a role in cell survival and generation of soluble nontoxic Aβ (sAPP) [237]. Levites *et al.* [238]

showed that EGCG at a lower concentration (1-5 μM) induced sAPP generation from human neuroblastoma and PC12 cells, whereas oral EGCG administration at the dose of 2 mg/kg/day increased the levels of PKCα and PKCε in the hippocampus of mouse models than control-treated animals [238]. In a study, Kaur *et al*. [239] used the passive avoidance test and reported that green tea extract (0.5%) administration for 8 weeks markedly ameliorated memory and learning of aged Wister rats. Effects of AChE in the cerebrum were found to be reduced in treated aged rat models than young rat models [239]. Kim *et al.* [240] observed that administration of 0.2% (*w*/*w*) tea PPH through diet reversed scopolamine-induced amnesia. In addition, tea PPHs also significantly suppressed the AChE activity [240].

6.4. Grape-Derived Polyphenols

Wine is the main product of grapes [241]. In Tg2576 mouse models, supplementation with Cabernet Sauvignon (a red wine) (had a very low level of resveratrol (0.2 mg/L)) markedly attenuated the Aβ neuropathology and AD-type impairment of spatial memory function as compared to control Tg2576 mouse models that received a comparable amount of water or ethanol alone [242]. Moderate consumption of this type of red wine also can increase α-secretase activity and αCTF level, which can eventually prevent the Aβ production and deposition [243]. It was reported that the levels of Aβ1-40 and Aβ1-42 were reduced in the hippocampus and neocortex of mouse models exposed to red wine [244]. Cabernet Sauvignon contains various PPHs, including catechins, tannic acid, and myricetin. These Cabernet Sauvignon-derived PPHs have strong fibril-destabilizing and anti-amyloidogenic activities, which indicate that these PPHs have a significant contribution to the neuroprotective properties of red wine. Resveratrol (a red wine-derived PPH) shows anti-amyloidogenic properties that might include its capacity to mediate Aβ clearance, instead of inhibition of Aβ generation [30]. Marambaud *et al.* [245] demonstrated that resveratrol did not affect the functions of β-and γ-secretases and did not block the generation of Aβ. Furthermore, these researchers observed that the capacity of resveratrol to destroy Aβ might include proteasome [245]. Cell death induced by Aβ was found to be dose-dependently decreased in the presence of co- and pre-treatments of resveratrol (15-40 μM) [13]. GF 109203X (a highly selective and potent inhibitor of protein kinase C (PKC)) pre-treatment markedly decreased the neuroprotective properties of resveratrol against Aβ25-35-induced cytotoxicity, whereas PD98059 (a highly selective MAP kinase inhibitor) and LY294002 (a potent inhibitor of PI3 kinase) did not modify the neuroprotective properties of resveratrol [246]. It has been indicated by western blot analysis that resveratrol (20-30 μM) triggered PKC phosphorylation and also eliminated the suppressive activity of Aβ25-35, which further indicates the function of PKC in the neuroprotective action of resveratrol [246]. Collectively, these results suggest that moderate consumption of red wine can decrease the risk of dementia and AD [247].

Quercetin (a wine-related PPH) significantly inhibited the *in vitro* formation of Aβ fibrils [248]. Ferulic acid (another wine-related PPH) did not avert the generation of fibrils, however, it altered the Aβ fibril lengths and provided protection against Aβ-induced toxicity in transgenic *Caenorhabditis elegans* [249]. Moreover, quercetin reversed Aβ-induced neurotoxicity and showed fibril-destabilizing properties on preformed Aβ fibrils in cells overexpressing APP Swedish mutation (APPswe), which is linked with early-onset FAD [250]. Quercetin-3-*O*-glucuronide (a polyphenol metabolite) has the capacity to affect the generation of neurotoxic oligomeric Aβ species. Consumption of Cabernet Sauvignon resulted in the accumulation of quercetin-3-*O*-glucuronide in the brains of rats and improvement in AD-related impairments *via* inducing neuroplasticity mechanisms [251]. In transgenic Tg2576 mouse models, Cabernet Sauvignon-derived wine consumption markedly inhibited AD phenotypes *via* averting the generation of Aβ [252].

Muscadine wine (derived from muscadine grapes) inhibited memory deficits in transgenic Tg2576 mice by interfering with the process of Aβ oligomerization [253]. Furthermore, the researchers observed in a Morris water maze (MWM) test that treatment with muscadine for 10 months markedly decreased the spatial memory impairment in around 14-month-old Tg2576 mouse models as compared to gender- and age-matched control, non-treated Tg2576 mouse models [253]. Resveratrol mainly acts *via* directly binding with Aβ and interfering with the aggregation of Aβ [254]. Resveratrol and its derivatives (found in wine), including ε-viniferin glucoside and piceid, significantly suppressed Aβ fibrillization and provided protection to PC12 cells against toxicities induced by Aβ [255]. In cell culture, ellagic acid (a wine-related PPH) reduced toxic intermediate oligomeric species and also decreased neurotoxicity induced by Aβ *via* inducing fibril formation [256].

In order to assess the protective properties of red wine, various studies have utilized the commercial grape seed polyphenolic extract (GSPE), which is a rich source of proanthocyanidins, gallic acid, and catechins. It was observed that GSPE markedly suppressed *in vitro* Aβ aggregation. Moreover, oral administration of GSPE reduced AD-type cognitive deficit and decreased Aβ plaques in an AD mouse model [257, 258]. It was suggested by the structural-activity relationships of GSPE compounds that the GSPE mixture contains the most effective PPHs that act as potent inhibitors of Aβ aggregation [259]. GSPE also inhibited the aggregations of tau and detachment of preformed tau aggregates, perhaps *via* non-covalent interactions of PPHs (derived from GSPE) with tau residues [260]. It was also reported that GSPE administration through drinking water markedly decreased the ameliorated motor phenotype and concentrations of toxic hyperphosporylated tau of transgenic mouse models expressing a human tau protein with P301L mutation [261]. Bioactive dietary polyphenol preparation (BDPP) is another grape-derived PPH that contains a combination of resveratrol, grape seed extract, and Concord grape juice. BDPP was found to mitigate cognitive deficit, loss of synaptic plasticity, and amyloid load in AD mice. Collectively, these findings suggest that combination treatment with extract preparation is more effective as compared to single PPH treatment [262].

Table 3. Summary of the purported effects of polyphenols in models of toxicity related to amyloid peptides.

Polyphenols	Study Model	Treatment Duration	Study Outcomes	Refs.
Curcumin	Aged APPsw Tg2576 mice	5 months	Reduced Aβ levels and plaque burden	[27]
	Parts of Tg2576 mouse brain	3-6 days	Suppressed Aβ aggregation; mediated disaggregation of Aβ	
	Neuronal hippocampal cultures	1 to 24 hours	Suppressed the generation of Aβ fibrils and fibril-destabilizing activities	
Resveratrol	Neuronal hippocampal cultures	2 hours	Blocked Aβ-induced toxicity	[30, 245, 246]
	Cells transfected with human APP695	24 hours	Mediated Aβ degradation	
	Neuronal hippocampal cultures	24 hours	Showed anti-amyloidogenic properties	
Myricetin	Neuronal hippocampal cultures	1 to 24 hours	Showed fibril-destabilizing properties; blocked Aβ(1-40)-induced toxicity; suppressed the generation of Aβ fibrils	[25]
EGCG	Neuronal hippocampal cultures	24-48 hours	Suppressed soluble forms of Aβ and Aβ fibrilization; blocked Aβ(1-42)-induced toxicity	[219, 263, 264]
	Tg APPsw mouse models	2 months	Reduced Aβ levels and Aβ plaques	
	C57/BL mouse models; human neuroblastoma cells	7-14 days	Elevated the levels of sAPP release; mediated non-amyloidogenic pathway	
Ellagic acid and Punicalagin	Tg APPsw/Tg2576 mouse models	6-8 months	Ameliorated AD-like pathology and behavior along with a reduced level of Aβ(1-42) and Aβ deposition	[172]
Gallic acid and tannic acid	Neuronal hippocampal cultures	1 to 24 hours	Showed fibril-destabilizing properties; blocked Aβ-induced toxicity; suppressed the generation of Aβ fibrils	[265]

7. STRUCTURE-ACTIVITY RELATIONSHIPS (SARs) OF Aβ-AGGREGATION INHIBITORS

A method of identification of potent inhibitors could be designing them according to natural compounds [266]. Various organic dyes, including curcumin, chrysamine G (CG), and congo red (CR) have the ability to strongly bind with Aβ [208, 267]. It has been reported that curcumin (widely found in turmeric) has the ability to suppress the formation of Aβ(1-40) and reduce its toxicity [267, 268]. CG, CR, and curcumin have a common chemical scaffold and they possess 2 substituted aromatic groups divided by a planar, rigid backbone (Fig. **4**).

Numerous studies have revealed that other curcumin-like ligands also suppress the aggregation of Aβ [269-277]. In order to identify the chemical properties crucial for inhibition, Reinke and Gestwicki [266] developed a library of small molecules. In order to develop the library, they gave importance to the molecules that look like CR and curcumin. The developed library addressed 3 components anticipated to influence activity (Fig. **5**). Firstly, curcumin's chemical scaffold, along with 2 aromatic end groups, is optimum for suppression and the *R1 portion deals with* whether compounds that have the deficiency of the second aromatic group preserve function. Secondly, substitutions on the phenyl groups are vital for the functions, thus the *R2* study deals with the activity of changing the hydrogen-bonding characteristics of these substitutions. Finally, the R3 substructure assesses the functions of flexibility and linker length. Collectively, even a slight alteration in any of the R1, R2, or R3 substructures has significant effects on function [266].

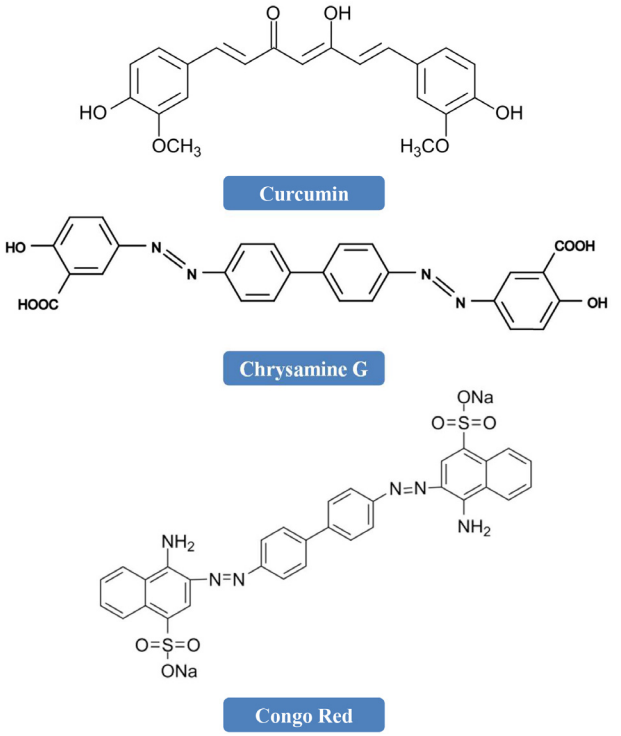

Fig. (4). Chemical structures of curcumin, chrysamine G, and congo red.

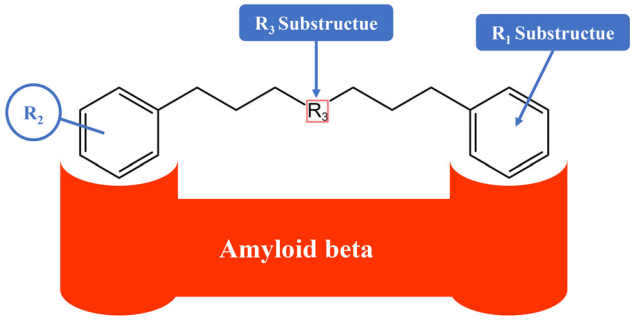

Fig. (5). Structural components that are essential for the function of Aβ-aggregation inhibitors [209]. [R_1 Substructue= a phenyl group; R_2 Substructue= a hydroxyl group; R_3 Substructue= linker length and flexibility [limited to 8 Å - 16 Å]. (*A higher resolution/colour version of this figure is available in the electronic copy of the article*).

8. FUTURE DIRECTIONS

Various mechanisms have already been indicated that are linked with PPH-induced protection from cytotoxicity mediated by amyloid assemblies. In this regard, for instance, resveratrol shows potent free radical scavenging activities in multiple cellular types [278, 279]. Various other PPHs also show antioxidant properties against NO-induced toxicity [25]. Along with the antioxidant properties of PPHs, multiple intracellular signaling pathways are also linked (at least partly) with their neuroprotective properties [25]. For instance, resveratrol induces MAP kinase activation in cells [280]. However, several researchers showed that *in vitro* suppression of Aβ generation is not reliant on oxidative environments. In addition, several researchers also revealed that structural properties of PPHs ought to be regarded as influencing their inhibitory function. Therefore, the antioxidant properties of PPHs might not offer a central mechanistic view for the suppressive mechanism by means of *in vitro* conditions. Interestingly, no correlation was detected between the antioxidant properties of the reported PPHs and *in vitro* inhibitory IC_{50} values. For instance, epicatechin is a potent antioxidant (2.54 times more potent than vitamin C) [281], however this PPH cannot effectively inhibit amyloid generation. Although morin exhibits relatively lower antioxidant properties (1.65 times higher as compared to vitamin C), however, morin can effectively inhibit Aβ [281]. Various studies have revealed that PPHs do not suppress cell death mediated *via* hydrogen peroxide or other OS factors [282-284]. Thus, a novel mechanistic technique is required, which will be reliant on structural similarities between multiple highly potent inhibitors of PPHs, and compared with the Congo red (an amyloidogenic dye). It has been observed that all the effective inhibitors of PPHs contain minimum 2 phenolic rings along with 2 to 6 atom linkers, and at least 3 OH groups attached to the aromatic rings. Collectively, these structural similarities indicate three-dimensional shapes that are vital for the non-covalent interaction with β-sheet structures, which are commonly observed in the case of all amyloidogenic structures. Furthermore, this interaction might only take place when the native conformation of the amyloidogenic proteins converts to the assembly conformation and cannot thus take place with the folded native protein [285-287].

CONCLUSION

There is growing evidence indicating that dietary intake of PPHs have the potential to decrease the occurrence of age-linked neurological disorders. Epidemiological studies have also indicated that there is an inverse link between the AD risk or cognitive deficit and the intake of PPHs-enriched vegetables, fruits, and beverages. Mechanisms of actions underlying the neuroprotective properties of PPHs are still not fully revealed. However, various PPHs, including turmeric-derived curcumin, tea-derived catechins, and grape-derived PPHs, have the capacity to inhibit the generation of Aβ fibrils and Aβ-oligomers. In addition, PPHs might also mediate Aβ clearance *via* playing roles on Aβ-degrading enzymes, including metallopeptidases or proteasomes. Collectively, the aforesaid results suggest that these PPHs might play roles as neuroprotective agents to prevent cognitive impairments. Moreover, future clinical trials are also required to assess the effectiveness of PPHs.

LIST OF ABBREVIATIONS

AD	=	Alzheimer's Disease
APP	=	Amyloid Precursor Protein
Aβ	=	Amyloid Beta
BDPP	=	Bioactive Dietary Polyphenol Preparation
CSF	=	Cerebrospinal Fluid
NDs	=	Neurodegenerative Diseases
OS	=	Oxidative Stress
ROS	=	Reactive Oxygen Species
UPR	=	Unfolded Protein Response

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CONFLICT OF INTEREST

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