HHS Public Access

Author manuscript

J Alzheimers Dis. Author manuscript; available in PMC 2021 June 29.

Published in final edited form as:

J Alzheimers Dis. 2021 ; 82(Suppl 1): S335–S357. doi:10.3233/JAD-200185.

Polyphenols as Potential Metal Chelation Compounds Against Alzheimer's Disease

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Abstract

Alzheimer's disease (AD) is the most common neurodegenerative disease affecting more than 50 million people worldwide. The pathology of this multifactorial disease is primarily characterized by the formation of amyloid-β (Aβ) aggregates; however, other etiological factors including metal dyshomeostasis, specifically copper (Cu), zinc (Zn), and iron (Fe), play critical role in disease progression. Because these transition metal ions are important for cellular function, their imbalance can cause oxidative stress that leads to cellular death and eventual cognitive decay. Importantly, these transition metal ions can interact with the amyloid-β protein precursor (AβPP) and $A\beta_{42}$ peptide, affecting Aβ aggregation and increasing its neurotoxicity. Considering how metal dyshomeostasis may substantially contribute to AD, this review discusses polyphenols and the underlying chemical principles that may enable them to act as natural chelators. Furthermore, polyphenols have various therapeutic effects, including antioxidant activity, metal chelation, mitochondrial function, and anti-amyloidogenic activity. These combined therapeutic effects of polyphenols make them strong candidates for a moderate chelation-based therapy for AD.

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Authors' disclosures available online (https://www.j-alz.com/manuscript-disclosures/20-0185r1).

Keywords

Alzheimer's disease; amyloid-β; metalloproteins; copper; zinc; iron; polyphenols; metal chelation therapy

INTRODUCTION

Neurodegenerative diseases (NDDs) are a consequence of progressive neuronal death which are typically associated with the accumulation of protein aggregates in the central nervous system (CNS), and eventually leading to loss of cognitive or motor function [1–3]. Although most NDDs are sporadic, approximately 10–20% of cases are caused by inherited mutations that sensitize carriers exposed to environmental factors [4, 5]. Alzheimer's disease (AD) is the most common NDD, followed by Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), Huntington's disease (HD), multiple sclerosis (MS), and prion diseases [6–13]. The etiology of NDDs is closely related to aging, but other factors are also involved, such as genomic instability, *de novo* and somatic mutations, epigenetic alterations, and environmental factors that include stressful situations, infections, and poor nutrition [4, 14]. NDDs may occur at specific sites or simultaneously in multiple regions of the brain [15, 16]. For example, the cerebral cortex and hippocampus are the two primary brain regions affected by neuronal loss [17]. In AD, neuronal loss mainly occurs in the nucleus basalis; in PD, the substantia nigra and striatum are the most affected by neuronal loss [15]. ALS usually affect the upper brain and lower spinal cord, whereas HD severely affects the striatal medium spiny neurons [15]. Although MS is generally associated with cortical demyelination, neuronal loss is reported in the basal ganglia, cerebellar cortex, spinal gray matter, and thalamus. In contrast, prion diseases can affect large areas of the brain, regardless of the origin of the prion [12–16].

AD is a devastating NDD that affects more than 50 million people worldwide, and its prevalence among the population between 65 and 85 years of age is estimated between 0.6% to 8.4% [18]. Furthermore, the 2018 World Alzheimer Report estimates that the number of cases will triple by 2050 [19, 20]. The main histological features that confirm AD are extracellular deposits of Aβ fibrils and intracellular neurofibrillary tangles (NFTs) [21]. The extracellular fibrils are composed of $A\beta_{42}$ peptides with a characteristic β-sheet structure, whereas NFTs are composed of phosphorylated tau protein [21, 22]. Other characteristic features of AD are the synaptic damage, mitochondrial dysfunction [23, 24], inflammation [25], and oxidation of biomolecules, and metal dyshomeostasis of calcium (Ca), copper (Cu), zinc (Zn), and iron (Fe) [22]. AD is identified by progressive memory loss, cognitive impairment, early neurovascular changes, accumulation of $A\beta_{42}$ peptide, tau protein tangles, and neuronal death [26, 27]. The etiology and pathology of AD is complex and multifactorial, where exogenous and endogenous factors can trigger the disorder [19]. Exogenous factors that may contribute to AD include lifestyle factors, including smoking, dietary deficiencies, and mental or physical inactivity. Chronic diseases, such as diabetes, obesity, and cardiovascular diseases are also linked to AD [28, 29]. Endogenous factors such as oxidative stress, metal ion dyshomeostasis, extra- and intracellular $A\beta_{42}$ peptide

concentration, and intracellular tau protein phosphorylation are related to AD progression [19].

There is evidence that essential metals, such as Cu, Zn, and Fe, are dysregulated in AD [30]. Of these biologically relevant transition metals, Cu receives the most attention because it interacts with both amyloid-β protein precursor (AβPP) and $A\beta_{42}$ peptide [31]. Furthermore, non-essential neurotoxic metals, such as aluminum (Al), lead (Pb), cadmium (Cd), and mercury (Hg), may have a role in triggering AD [31–33]. Cu and Fe both increase the production of reactive oxygen species (ROS), causing neuronal death and subsequent cognitive defects [4]. Zn modulates Cu binding to $A\beta_{42}$ peptide, thus indirectly affecting ROS production. Additionally, AβPP and $A\beta_{42}$ peptide are metalloproteins that have the ability to sequester metal ions, and the resulting complex can increase the redox toxicity and induce Aβ aggregation [30–33]. Unbound Cu and Fe ions can also react with hydrogen peroxide (H_2O_2) and generate hydroxyl radicals ($HO^{\bullet}$) through a Fenton reaction mechanism, thus causing oxidative stress to cells [4, 34–39]. For these reasons, we speculate that metal imbalance is closely linked to AD pathogenesis. A major challenge to discovering new drugs against AD is the lack of an animal model that reflects the entirety of AD pathology, as well as the lack of biomarker specificity [40, 41]. There is an urgent need to discover new drugs that can prevent or halt AD progression.

Investigations of AD etiology have uncovered many factors that contribute to AD progression. Due to the complexity of AD contributing factors, there are many promising multifunctional compounds for targeting these different pathological components in a parallel fashion [42]. Thus, the interest in natural products, specifically the large family of polyphenols, is based on current investigations that demonstrate therapeutic properties such as antioxidant, anti-amyloidogenic activity, cell signaling modulation, and metal chelation activity (Fig. 1) [43–45]. Polyphenols have also been demonstrated to have neuroprotective activity against AD [1, 46], PD [24, 47–50], HD [51, 52], and ALS [53, 54]. Metal chelation is a promising avenue for research due to increasing evidence of metal dyshomeostasis in AD; however, massive chelation as an approach may not be favorable because it could disrupt normal metalloproteins activity [45, 55]. Alternatively, chelation could be mediated by molecules with moderate yet specific affinities for targeted transition metals, thus reducing the neurotoxic effects caused by interaction between the metals and $A\beta_{42}$ peptide [56, 57]. Such classes of emerging compounds are referred to as metal-protein attenuating compounds (MPACs) [55–58]. This review will focus on the chelating properties of polyphenols that are natural sources of potential MPACs and discuss their potential therapeutic effects in mitigating metal ion dyshomeostasis in a moderate chelation treatment for AD. We are focused on Cu, Zn, and Fe because these *d*-block transition metals are essential to humans, relatively abundant in the CNS, and involved in AD triggering.

LEVELS OF TRANSITION METAL IONS IN THE BRAIN

Transition metal ions with accessible *d* orbitals are necessary for critical biological processes, including oxygen transport, oxygen activation, neurotransmitter synthesis, DNA replication and transcription, cell-cell interactions, and extracellular matrix construction and demolition [59–62]. In these processes, metal ions are structural and metabolic cofactors, as

well as electron transporters. Metalloproteins such as ceruloplasmin, superoxide dismutase, hemoglobin, and cobalamin contain the transition metals Cu, Zn, Fe, cobalt (Co), and manganese (Mn) [30, 62, 63]. Exposure to environmental metals such as Mn, Cu, Zn, Fe, Pb, Hg, and Al, is a risk factor for NDDs [64, 65]. For example, excess Fe and inhalation of Mn dust are linked to PD [66]. Also, essential metals (Cu, Zn, and Fe) and non-essential metals (Al) are major contributors to AD and PD pathophysiology [37, 66]. In AD brains, Cu concentrations are as high as 400 μM and Zn concentrations reach 1 mM, which are much higher than the acknowledged healthy concentrations of Cu (70 μM) and Zn (350 μM) [37, 67]. Both Cu and Zn metabolism are regulated by metallothioneins and an antagonistic relationship may exist between Cu and Zn [17, 33]. In AD, metallothionein I and II are upregulated, further suggesting an inverse relationship between Cu and Zn. This phenomenon is most notable in the metal-rich hippocampus and amygdala. In AD, transition metal ions, notably Cu, Zn, and Fe, first accumulate on Aβ fibrils. Moreover, these metals have roles in both Aβ fibril and tautangles aggregation that may be attributed to their oxophilic character. Because d-block transition metal ions have neurodegenerative effects on the brain, their role in AD is of high interest [17, 68–70].

Copper levels

Cu(II) has a d^9 electron configuration, which distorts the octahedral orientation in a Jahn-Teller manner and stabilizes square planar formation [17, 71]. Protein binding distorts the configuration of Cu(II) complexes in a way that is important for regulating Cu catalysis both in cells and in the extracellular space. In the body, extracellular Cu(II) is attached to cysteine (Cys) and histidine (His) sidechains. Inside cells under normal conditions, Cu is almost in the reduced form Cu(I) and tightly bound to proteins [72]. Because Cu is a redox active transition metal ion involved in dioxygen and peroxide activation, its role in producing and clearing ROS in the CNS is not surprising [73, 74]. Indeed, in AD pathogenesis, light metal ions, such as Fe and Zn, compete for the active and transporter sites of concentrated Cu ions [75, 76].

Cu transporter 1 (CTR1) and Cu ATPases (ATP7A and ATP7B) are responsible for intracellular Cu(I) regulation, whereas the divalent metal transporter 1 (DMT1) is involved in regulating Cu(II) [77]. Healthy serum levels of Cu range between 1020–1050 μg/L [70], whereas serum levels of unbound Cu in AD patients tend to be higher; these higher Cu serum levels are attributed to disrupted ion transport [78]. Excess Cu produces abnormal behavior involved in the development of NDDs. Menkes and Wilson's diseases are examples of how disruption of metal ion homeostasis can be detrimental [66]. In Menkes disease, a mutation in ATP7A causes Cu deficiency in the cerebellum region [79]. In contrast, Wilson's disease occurs when an ATP7B mutation causes excess Cu in the basal ganglia area, leading to Cu toxicity [79–81]. Nonetheless, both disorders are congenital and of particular research interest because these were the first NDDs linked to Cu metabolism.

Cu is frequently studied because AD manifests in both disruption regions of the metal ion, but primarily in cortical gray matter where Aβ fibrils and neurofibrillary tangles are found [69]. During short-term alterations of Cu levels, metal-binding proteins, such as metallothionein and ceruloplasmin, act as buffers. However, during a long-term increase of

Cu concentration, metal binding proteins are unregulated to prevent further toxicity. After a critical concentration is reached, free circulating Cu levels increase. Additionally, when Cu is bound to smaller proteins, it can cross the blood-brain barrier (BBB) and cause neurotoxic effects such as $A\beta_{42}$ aggregation and also change DNA conformation. DNA conformation changes may be caused by interactions between the Aβ-Cu complex and trinucleotides CAG and CTG, which disrupt the B conformation of DNA and create cellular instability [82].

Zinc levels

Zn(II) has a closed shell d^{10} diamagnetic electron configuration, similar to Cu(I) [83, 84]. However, the ionization energy of Zn(II) is too large to reach oxidized states. Zn usually exists in tetrahedral or octahedral orientations, but also forms pentagonal complexes with bipyramidal trigonal and square pyramidal configurations. Because of its closed *d* shell, Zn(II) has a high positive charge density, even compared to Ca(II). This property allows Zn(II) to bind to proteins and nucleic acids, acting as an important structural component in many proteins and as a co-factor for more than 300 enzymes [85]. Zn(II) contributes to regulating cellular processes and signaling pathways because a high positive charge makes Zn(II) a strong Lewis acid, particularly in hydrolysis reactions. In the brain, Zn(II) is found within synaptic vesicles and glutamatergic terminals. Similar to Cu, Zn(II) dysregulation causes neurotoxic effects, including DNA nicking and affecting $A\beta_{42}$ aggregation [40, 85]. Zn(II) homeostasis is regulated by three different groups of macromolecules: Zn transporters, Zn-regulated, and Fe-regulated transporter proteins, and metallothioneins [77, 85]. Zn metallothioneins have four isoforms; of these, metallothionein III is brain specific and is found with Zn in astrocytes, neurons, and synaptic vesicles. Healthy serum levels of Zn range between 720–899 μg/L [70, 86]. However, a meta-analysis of Zn serum levels in 1027 AD patients and 1949 healthy people as controls found discordant results. Nonetheless, the analysis concluded that Zn levels are lower in patients with AD [69] and other meta-analyses have reached the same conclusion [31, 86, 87].

Iron levels

Like Cu, Fe has two major oxidation states in the body, Fe(II) and Fe(III). Cycling between the two oxidation states occurs easily because they differ by a single electron. Fe and Cu are Fenton catalysts affecting ROS levels [88–91]. In cells, the reduced form of Fe is usually stabilized by heme group binding and formation of a distorted octahedron by two axial ligands [59, 60, 92]. Fe has many electron spin states and several different configurations, including tetrahedral; however, an octahedral shape is common for both oxidation states [91]. An oxidation-reduction state can cause neurotoxic effects, such as affecting the production, folding, and aggregation of proteins, but, when this property holds, transition metal ions have essential roles in DNA synthesis, neurotransmission, and oxygen transport. Transition metal ions also act as cofactors for key enzymes in the biosynthesis of neurotransmitters, such as dopamine and noradrenaline [39, 88]. The controlled transport of Fe is mediated by proteins that undergo a series of oxidations and reductions. For instance, ceruloplasmin oxidation is required for Fe transport by transferrin. Other proteins, such as DMT1 and ferroportin, are involved in Fe transport, whereas ferritin controls Fe storage. The accumulation of Fe in neurodegenerative sites may be attributed to altered levels of ferritin and transferrin that decrease export of metal ions from cells [86, 93]. Ferroptosis, an

apoptotic pathway related to increased Fe concentration in cells, is triggered regardless of ROS production and is linked to neurodegeneration [58, 65]. Additionally, meta-analyses have shown lower Fe serum levels in AD patients than in healthy counterparts, which range between 633–2444.4 μg/L [69, 86].

ALZHEIMER'S DISEASE AND TRANSITION METAL IONS IN THE BRAIN

AβPP is a multidomain transmembrane glycoprotein and the most common isoforms have 695, 751, and 770 amino acid (aa) residues [89, 94]. AβPP has two Cu binding sites, one between residues 124 and 189, and another at the E2 domain between residues 376 and 554. The first domain is formed by two histidine residues (His147 and His151), one tyrosine residue (Tyr168), and two water molecules. Together these form a pentagonal complex with Cu(II) in a non-planar orientation, favoring reduction to Cu(I) (Fig. 2a)[95]. After Cu reduction, a disulfide bridge forms between neighboring cysteine residues (Cys144 and Cys158) [36]. The second domain is formed by four histidine residues (His388, His457, His507, and His511). The tetra-coordinated complex with Cu(II) distorts the square planar geometry, leading to a structural change in AβPP (Fig. 2b)[96]. AβPP can be cleaved by α-, β-, and γ-secretases, and cleaving leads to two pathways: non-amyloidogenic and amyloidogenic [97]. In the first pathway, AβPP is cleaved in the middle of the Aβ sequence region by α-secretase (a disintegrin and metalloproteinase) at Lys687, resulting in a secreted AβPPα fragment (sAβPPα) and a C-terminal fragment (CTFα) [98]. Further cleaving of CTFα by γ-secretase leads to formation of protein 3 (p3), a soluble and neuroprotective peptide [99, 100]. In the second pathway, AβPP is cleaved past Met671 by β-secretase, forming a secreted AβPPβ fragment (sAβPPβ) and a C-terminal fragment (CTFβ) [101]. CTFβ is then cleaved by γ-secretase producing the $A\beta_{42}$ peptide in one of two isoforms, $A\beta_{40}$ or $A\beta_{42}$, and $A\beta_{42}$ aggregates at a higher rate [102]. Recently, the composition of Aβ fibrils has been revised, so that the recognized percentage of N-truncated $A\beta_{42}$ peptides is increased [103, 104].

AβPP and $A\beta_{42}$ peptide could be considered metalloproteins because they sequester transition metal ions, as shown by nuclear magnetic resonance (NMR), electron spin resonance (ESR), and crystallography results [36, 105, 106]. When $A\beta_{42}$ peptide is formed, a new Cu binding site is created with His6, His13, and His14 residues and the controversial keto-moieties of Ala2. At this binding site, Cu binding has a square planar orientation (Fig. 2c) [107, 108]. Another proposed binding orientation based on X-ray absorption spectroscopy (XAS) indicated the existence of a five-coordinated complex formed by three histidine residues (His6, His13, His14), one tyrosine (Tyr10), and one water molecule (Fig. 2d) [109–111]. Finally, IR spectroscopy suggests that carboxylate groups of aspartate (Asp1 or Asp7) or glutamate (Glu3 or Glu11) interact with transition metals instead of Tyr10 (Fig. 2e) [112, 113]. Because the $A\beta_{42}$ ligand is disordered, the high valence Cu(II) orientation is highly dynamic, which has important implications for the mechanism of redox cycling and Cu reactivity [114, 115].

$A\beta_{42}$ peptides have four basic interactions, three of which correspond to the imidazol ring of His6, His13, and His14 [64]. The fourth interaction is based on the nucleophilic (or Lewis base) character and size of the residue, which increases the possibility of interacting with a

metal. The phenol group of Tyr10 is nucleophilic and larger than the carboxylate groups of either aspartate (Asp1 or Asp7) or glutamate (Glu3 or Glu11) residues, allowing it to interact with the metal. The hydroxyl group of Tyr10 (pKa~10) could become deprotonated by water due to interaction with the metal ion or from hydrogen bonds with neighboring residues. For these reasons, Tyr10 has a greater probability of interacting with the metal than as part ate (Asp1 or Asp7) and glutamate (Glu3 or Glu11) residues (Fig. 2d). However, interaction with metal ions increases the acidity of amide groups, which compete as ligands for the metal ion [92]. Although more complex stoichiometry is reported, it is generally accepted that the stoichiometry of $A\beta_{40/42}$–Cu^{2+} complexes is generally a 1 : 1 molar ratio [30, 116].

According to the amyloid-β hypothesis of AD, the $A\beta_{42}$ peptide is implicated in AD progression, such that an imbalance between $A\beta_{42}$ production and clearance triggers AD pathogenesis in the human brain [21, 117]. This hypothesis is supported by experimental results showing that mutations in genes encoding for AβPP, presenilin 1 or 2 (PS1 or PS2), or Apolipoprotein E allele 4 (APOEε4), lead to accumulation of $A\beta_{42}$ in the brain [118–120]. $A\beta_{42}$ aggregation in the brain is considered the hallmark of AD [119, 121]. $A\beta_{42}$ fibril formation is a multistep process that starts with monomers, followed by oligomers, protofibrils, and eventually mature fibrils [21, 122, 123]. Furthermore, $A\beta_{42}$ aggregation induced by transition metal ions produce ROS such as H_2O_2 [124]. Soluble oligomers are considered neurotoxic because they can induce dyshomeostasis, oxidative injury, inflammation, and the development of tau protein tangles [15, 40, 125].

It is important to understand the close relationship between oxidation-reduction cycles and transition metal ion activity in $A\beta_{42}$ aggregation. Here, we focus on how transition metal ions affect $A\beta_{42}$ aggregation and ROS production by forming an Aβ-metal complex.

Effects of transition metal ions on $A\beta_{42}$ aggregation

Transition metal ions may promote aggregation of $A\beta_{42}$ peptide [126]. Surface plasmon resonance experiments show that the aggregation constant k_a increases when Cu(II), Zn(II), and Fe(III) are added to growth media [127, 128]. Of the three transition metal ions, Cu(II) addition resulted in the largest k_a increase(13.6-fold) compared to $A\beta_{42}$ aggregation alone. Moreover, Cu(II) may preferentially bind monomers and small oligomers of the peptide, whereas Zn(II) promotes formation of larger aggregates. Thus, Cu(II) and Zn(II) may have different mechanisms to induce aggregation. Zn(II) also induces aggregation of $A\beta_{42}$ peptides by promoting a conformation change from the α-helix intermediate to a larger β-sheet structure [129]. In contrast, Cu(II) may increase toxicity by stabilizing intermediate aggregates [116].

$A\beta_{42}$ monomers have a mostly random-coil structure that evolves into β-sheet structure as the fibrillization progresses [130]. However, transition metal ions affect peptide aggregation by changing $A\beta_{42}$ conformation and interpeptide connectivity. For example, Cu catalyzes dimer formation via a dityrosine product of radical chemistry [111, 129, 131, 132]. Moreover, NMR spectroscopy and surface plasmon resonance experiments have shown that intermolecular complexes form via Zn(II)-induced oligomerization [133, 134]. These studies indicate that His6, His13, and aa residues 11–14 are the crucial residues involved in forming the seeding dimer. Furthermore, both Zn and Cu induce amorphous aggregation while

inhibiting formation of β-sheets [116, 129, 135]. This amorphous quality is confirmed by chromatographic and NMR studies, which also suggest that the Aβ-Cu/Zn building block is monomeric during oligomerization and subsequent metal ion reshuffling [129]. In addition to amorphous aggregates, a granular has been identified only in the presence of metal ions [136]. Because $A\beta_{42}$ is a disordered protein, it is affected by changes in the population of thermally accessible $A\beta_{42}$ conformers in disordered chains. These population changes are induced by interactions with transition metal ions or by the chain environment [137, 138]. This issue has been investigated for $A\beta_{42}$ using MS and solid state NMR [139, 140].

ROS production by Aβ-metal complex interaction

Oxidative stress caused by Fenton and Haber-Weiss reactions produces ROS and reactive nitrogen species that play a key role in degenerative diseases [141]. Transition metal ions catalyze reactions that produce radicals that damage DNA, proteins, and lipids. In AD, hydroxyl radicals produced by Fe(III) cause $A\beta_{42}$ neurotoxicity and turn soluble fibrinogen into insoluble aggregates [141]. There are higher concentrations of Fe in AD plaques (1 mM) than in healthy brain tissue (350 μM). Also, Fe affects $A\beta_{42}$ aggregation and tau phosphorylation [141]. In ROS chemistry, the hydroxyl radical is the most aggressive [142–144]. Hydroxyl radicals are formed when each one-electron transfer step is facilitated by a single electron reductant like ascorbate, and an ion like Cu or Femediates one-electron transfer, with the Fenton reaction as the last step (Fig. 3).

Dioxygen is formed by splitting the triplet state of dioxygen into two radicals (two doublet species) [115]. This transient species is a Cu(I) complex that is produced in small amounts by reducing molecules, much like Fe(II) species in Fenton chemistry [143]. Splitting produces Cu(II) and superoxide, both in doublet spin states. Reducing agents are abundant in cells and synapses [145]. The most representative reducing agent is ascorbic acid, which is chemically similar to polyphenols, but characterized by greater solubility in water and a lower first dissociation pKa constant. Ascorbic acid (DH_2) at pH~7 is almost completely dissociated into ascorbate (DH^-) and one-electron oxidation produces an ascorbyl radical ($DH^\bullet$). DH is easily oxidized into dehydroascorbic acid, the 2-electron oxidized form of ascorbic acid (D), which is actively transported through BBB [145].

The first step in Fig. 3 is the inverted initial part of a Haber-Weiss reaction, where oxidation of Fe(II) to Fe(III) is mediated by an initial amount of superoxide [141]. The direction of this step depends on the amount of reducing agent (ascorbate is more abundant in the synapse than superoxide) and on binding between the ligand and transition metal ion. Notably, high valence transition metal ions, Cu(II) or Fe(III), can be destabilized by geometrical distortions when the ligand binding is not rigid. Indeed, Aβ is an intrinsically disordered peptide. The pro-oxidant role of Aβ-Cu(II) is based on Cu binding to Aβ because this phenomenon catalyzes ROS production [131]. Aβ-Cu(II) intermediates produce more hydroxyl radicals ($OH^\bullet$) and H_2O_2 than monomeric Aβ-Cu(II), supporting the hypothesis that aggregation intermediates are more toxic than fibrils [126, 129]. Comparison of ROS production kinetics of the Aβ-Cu(II) complex in the presence of ascorbate with those of physiologically normal Cu complexes, such as those formed with aa, albumin, and metallothionenin III, showed that Aβ-Cu(II) produced more hydroxyl radicals than the other

complexes [146, 147]. Similarly, studies comparing the production of H_2O_2 by $A\beta_{42}$ monomers, oligomers, and fibrils, in the presence of Cu(II), showed that oligomers produced more ROS than the other two forms, supporting the hypothesis that oligomers are the main source of ROS generation [148]. The first step in ROS production catalyzed by Aβ-Cu is the *in situ* reduction of dioxygen to super-oxide ($O_2^{\bullet-}$) [115, 149–151]. Superoxide rapidly attacks other sites in the $A\beta_{42}$ peptide and the environment, including sites that stabilize pre-organized oligomers by forming covalent bonds [132, 147, 152]. Thus, the oxidative damage in AD may be due to prooxidant activity of Aβ-Cu(II) complexes. ROS effects include the oxidation of the $A\beta_{42}$ peptide, including decarboxylation and deamination of Asp1, oxidation of histidine and methionine, and cleavage of the main $A\beta_{42}$ chain [111, 131, 153].

Characterization of the Aβ-Fe(II/III) complex is more complicated. *In vitro* experiments show that in the reduced form, Fe binds the $A\beta_{42}$ monomer in a 1 : 1 ratio, but oxidized Fe becomes intercalated with monomers, indicating an extended intermolecular Fe-mediated interaction network [141, 153, 154]. Indeed, these results are consistent with *in vivo* observations of nanostructured FeO particles that co-localized with $A\beta_{42}$ aggregates [155]. Zn(II) is assumed to be neuroprotective, compared to Cu(II) and Fe(III), due to its displacement effect on redox-active metal ions. Indeed, in contrast to redox active metal ions, Zn(II) decreases neurotoxic effects in cell culture [111]. A proposed mechanism for the neuroprotective effects of Zn(II) is a metal swap between a Zn(II)-loaded metallothionein III and the Aβ-Cu(II) complex, thus reducing ROS production. However, a reported down-regulation of metallothionein III in AD would prevent the metal swap and increase neurotoxic effects of the Aβ-Cu(II) complex [129].

METAL CHELATION THERAPY

Metal chelation is a prominent therapy for dyshomeostasis of transition metal ions in the brain and could be used to prevent production of toxic $A\beta_{42}$ species and ROS [156]. Transition metal ions in free form are highly toxic and usually tightly bound to proteins; therefore, chelation is an essential therapy to control metal ion levels during conditions where metals are more likely to be released from proteins [33, 157]. Chelators have a high binding affinity for metals, and metal chelation therapy is used for heavy metal poisoning and diseases caused by an excess of metal ions [158, 159]. However, because chelation therapy has low specificity and many side effects, few chelating compounds are approved by the FDA (Fig. 4), [160, 161]. Dithiol BAL (British Anti-Lewisite) was developed during World War II and is used to treat arsenic, mercury, and lead poisoning [162]. Similarly, calcium-EDTA is only used for heavy metal poisoning, and is used in conjunction with BAL for acute lead poisoning [160]. However, because BAL has hypertension, nausea, and vomiting as side effects, synthetic derivatives with less severe side effects have been developed [163]. DMSA, better known as succimer, is a BAL-derivative approved for treating lead poisoning in children [160]. The main advantage of succimeris its reduced toxicity, which makes it suitable for long-term administration and able to decrease lead and methylmercury deposits in the brain [162]. Another thiol-containing chelating agent is d-penicillamine (DPA), which is approved for treating Wilson’s disease and available in oral form [160]. DPA is effective for rapid elimination of Cu through urine, and is given in combination with Zn salts to promote metallothionein synthesis [81]. Similarly, clinically

licensed Fe chelators are used to treat Fe overload caused by frequent blood transfusions in patients with genetic blood diseases. The standard Fe chelator is deferoxamine (DFOA), which is highly efficient due to its shielding effect on metal ions that prevents it from being reduced [162]. However, DFOA is inconvenient to administer, so a combined therapy of deferiprone (DFP) and deferasirox (DFX) is also available [164]. Metal chelation therapy is used in very specific circumstances, and chelation in AD must be applied differently than the classic approach of massive chelation [165]. A major challenge for metal chelation in AD arises from the need for the chelation compound to cross the BBB, which requires a hydrophobic and low molecular weight chelator [165, 166]. Clinically available chelators are hydrophilic and intended to act on tissues; therefore, these are not suitable therapeutic molecules for AD [158, 159, 167]. Another challenge is that chelation for AD treatment must avoid complete depletion of biometals, because biometals have essential neurological roles in metalloproteins activity [157, 158, 165–168].

Potential chelators of interest for AD therapy have been called metal-protein attenuating compounds (MPACs). MPACs should have specific and moderate chelation activity to prevent metal depletion [56, 165, 166, 168–172]. The main difference between metal chelators and MPACs is the binding constant, which should be weaker in MPACs than in traditional chelators [173]. Also, metal chelation therapy for AD should focus on redistributing metals to interrupt abnormal metal-protein interactions, rather than excreting metals from the brain [165, 169]. Additional challenges to metal chelation therapy for AD include understanding potential metal-chelator complexes and anticipating how disaggregated $A\beta_{42}$ peptides will be diverted from pathological pathways [165, 174]. Considering these requirements, hydroxyquinolines are potential MPACs [173]. Clioquinol, an 8-hydroxyquinoline derivative, is a hydrophobic molecule with therapeutic activity in AD, including solubilizing the Cu(II)/Zn(II)-Aβ complex, inhibiting $A\beta_{42}$ aggregation, and decreasing redox toxicity [164, 168, 175, 176]. However, the safety of clioquinol as an AD treatment is still undetermined [172, 174, 177–179]. Clioquinol has a hydroxyl and amine moieties which coordinate with Cu(II) and Zn(II) to form a stable five-membered ring [168, 180]. PBT2 is another hydroxyquinoline derivative that has undergone phase II clinical trials for AD treatment [181, 182]. PBT2 chelates Cu(II) and Zn(II) ions trapped between Aβ fibrils, and facilitates re-uptake of ions into cells [182]. Despite these favorable results, PBT2 is no longer being as an AD therapy; however, it is currently researched as a drug for HD [183].

Polyphenols as metal chelators in Alzheimer's disease

Polyphenols are natural compounds that are abundant in fruits, vegetables, and seeds [1, 184]. These compounds possess several nutrition benefits to protect against heart disease, diabetes, and brain disorders [3, 185, 186]. Polyphenols from dietary origin are considered safe for most consumers but the consumption of fortified food or supplements need to be carefully regulated. The fortified food or supplements containing the high quantity of polyphenols can trigger undesirable effects such as adverse interaction with medications, kidney damage, increase stroke, mortality, etc. [187, 188]. As nutraceutical compounds polyphenols can be used as preventive strategy or to mitigate decrease progression [189–191]. Naturally occurring polyphenols, such as curcumin, epigallocatechin-3-gallate

(EGCG), quercetin, myricetin, and others, are considered candidate therapeutics for AD and other diseases [3, 156]. Curcumin, which is found in *Turmeric longa*, appears to have therapeutic activity, including anti-inflammatory, neurotoxic metal chelating, neuroprotective, anti-amyloidogenic, and reducing oxidative damage to mitochondria and DNA [192–197]. Epidemiological studies demonstrate that the curcumin consumption can decrease the incidence of AD 4.4 times [198]. Significantly reduced AD incidence rate in the south asian and indian people is thought to be attributed to the abundant use of turmeric as an important spice in indian diet, which supports this hypothesis [198]. Curcumin chelates Cu and Fe transition ions, which play roles in AD pathology [156, 196, 199]. The keto-enol moiety is crucial for metal coordination [200, 201]. Additionally, the hydroxyl groups of curcumin interact with ROS to form a stable species that does not damage DNA [202]. EGCG is the most abundant catechin found in the green tea plant *Camellia sinensis*. The green tea plant has antioxidant, metal chelating, anti-inflammatory, anti-carcinogenic, and anti-apoptotic properties [46, 203, 204]. EGCG sequesters Fe and Cu transition ions, which increases its potential as a neuroprotective treatment [205, 206]. EGCG forms two five-membered stable rings with transition metals found at hydroxyl groups in ring B and at the gallic acid moiety, thus preventing ROS production [203, 206, 207]. The effects of EGCG on Aβ aggregation in the presence of Cu(II) have been explored with electrochemical and optical techniques, and the results were concordant with thioflavin-T assays [208]. A decrease in the electrochemical signal in a square wave voltammetry experiment indicated chelation of Cu(II), whereas TEM imaging showed unstructured aggregates, unlike the structured aggregates that formed in the absence of polyphenol [208]. These results suggest that the anti-aggregation potential of EGCG is due to Cu(II) chelation, which prevents the Cu(II) ion from interacting with His residues in the peptide [208]. Quercetin and myricetin are promising therapeutic candidates due to their bifunctionality as antioxidants and chelating molecules [209, 210]. Structures of quercetin and myricetin indicate three potential metal binding sites. A six-membered aromatic ring forms at the β-ketophenolate (5-hydroxy-4-keto site), whereas a five-membered ring forms at the α-ketoenolate (3-hydroxy-4-keto site). The third metal binding site involves the catechol moieties, which exhibit antioxidant and chelating activities [211]. However, there is controversy surrounding the β-ketophenolate and α-ketoenolate binding sites of flavonoids. There is evidence of interactions between the β-ketophenolate moiety of flaviolin and the active-site metal in cytochrome P450 [212]. In contrast, there is evidence of preferred binding between the α-ketoenolate moiety of quercetin and Cu(II)-Aβ, indicating different modes of metal binding in the flavonoids group [211]. Additionally, computer models suggest that Cu(II) binds quercetin, indicating that the α-ketoenolate site is the most probable chelation site [210]. However, the catechol binding site is considered to have the highest metal binding affinity [213].

Chelators characteristic of polyphenols

Polyphenols are metal chelators with high therapeutic potential, suggested by their characteristic coordination with oxophilic transition metals that forms stable five- or six-membered rings [156, 196, 199, 214–216]. The metal chelation potential of polyphenols strongly depends on the catechol moieties and combinations of hydroxyl and carbonyl groups [217, 218]. Combinations of these groups and moieties define metal binding sites.

Therefore, we propose that polyphenols be classified into three groups (Fig. 5). Most polyphenols would be included in a “one-metal binding site” group, because they have only one potential chelator site. This group includes curcuminoids, lignans, still-benes, isoflavonoids, flavanols, and anthocyanins. A “two-metal binding sites” group includes flavones and flavanones. A “three-metal binding sites” group includes flavonols, flavanols, and tannins. This classification also strongly depends on the type of substitutions, as previously reviewed [1, 213]. Investigations suggest that the therapeutic efficacy of polyphenols in preventing metal-free and metal-induced $A\beta_{42}$ aggregation is proportional to the number of catechol moieties present in the therapeutic compound [219]. However, in polyphenols with overlapping metal binding sites, such as the pyrogallol group in delphinidin (Fig. 5), only one of the potential binding sites may chelate, due to disruption of an adjacent site [213].

Chelation therapy exploits physical and chemical properties of metals, such as the principles of Pearson, ionic radius, solvation, chemical stability, bioavailability, metabolism, and natural excretion [162, 174]. Among these, the principles of Pearson explain the driving forces behind chelation therapy. The principles of Pearson or Hard-Soft Acid-Base (HSAB) Theory state that Lewis acids and bases can be considered “hard” or “soft” based on their ion size and polarizability [220]. A “hard” molecule is any species that is small and slightly polarized, whereas a “soft” molecule is larger in size and more polarized. Moreover, Pearson states that hard species tend to couple with hard species electrostatically, with a mostly ionic bond character. Soft species couple with soft species, with electron exchange and/or electron density changes dominated by covalent and/or dispersive nonbonding interactions [220]. Thus, the stability of metal chelate complexes is determined by the hardness/softness of ligands and ions [163]. Generally, ligands are hard bases containing electron donors that are oxygen or nitrogen groups, such as hydroxyl, carboxylate or amine moieties [163, 221]. However, this classification does not clearly divide “hard” and “soft” ligands and ions, because there are also “intermediate” species. For example, transition metal ions involved in AD pathology are intermediate acids with a hardness that decreases with size [Fe(II) > Cu(II) > Zn(II)] [222]. This intermediate nature of transition metals ions is important because it allows them to interact with both “hard” and “soft” bases. Unoccupied *d* orbitals of transition metal ions can be filled by a basic ligand to form a highly stable and soluble metal complex, thus introducing metal binding chemistry into biological processes [83, 84, 91]. In addition to the formation of coordination bonds, chelation involves formation of stable rings because fewer geometrical constraints arise from the metal-ligand bond (due to the involvement of *d* orbitals) in contrast to C-C or C-N bonds [223].

The principles of Pearson can be used to describe polyphenols as chelating molecule. Any deprotonated phenolic group will reveal an oxygen with a high charge density, thus resulting in a “hard” ligand [213, 216]. The relatively high pKa of phenols (~9–10) decreases (to ~5–8) because the proton is displaced by metals, such as Fe(III) and Cu(II) [92]. Thus, metal chelation by polyphenols occurs at pH 7.4 [200, 213]. The phenolic pKa value is important for metal chelation, because metal chelation is more efficient at lower pK_a values [224]. We also consider that the binding of a metal ion to a polyphenol is favored by oxophilic attraction between a metal and “hard” deprotonated oxygen atoms, creating a stable five- or six-membered ring (Fig. 6) [216]. For example, curcuminoids form a stable six-membered

ring with transition metals due to curcuminoid keto groups, which have enolic tautomer of acetylacetone properties [225, 226]. Similarly, genistein and luteolin form six-membered rings with transition metals via their adjacent 5-hydroxyl and keto groups. Five-membered rings are formed by the catechol moieties in piceatannol, delphinidin, and EGCG. Flavanones, flavones, and flavonols, such as eriodictyol, baicilein, and myricetin, also form stable five- and six-member heterocycle rings with transition metals [63, 174, 227]. An electrospray mass spectrometry study showed that Cu and Fe are chelated by some flavonoids, including kaempferol, quercetin, myricetin, luteolin, naringenin, and catechin. The stoichiometry for Cu(II)/flavonoid ratios is usually 1 : 1 and 1 : 2, whereas those for Fe(II) vary among studied polyphenols. In Fe(II) chelation stoichiometry, the reducing ability of the chelation compound increases with the number of hydroxyl groups (myricetin > quercetin > catechin > luteolin > kaempferol > naringenin). The study concluded that the 4-oxo, 3- and 5-hydroxyl groups, and *ortho*-catechol groups are the metal chelating sites in these molecules [228]. Additionally, Cu and Fe metal chelation assays have shown that polyphenols have moderate to strong chelating activity [224, 229, 230].

Polyphenols interact with transition metal ions

During ROS production in the synaptic cleft, antioxidants disrupt the initiating reaction and scavenge the free radicals created by propagation reactions, such as Fenton and Haber-Weiss reactions (Fig. 7) [144, 218]. Polyphenols have antioxidant effects due to phenolic hydroxyl groups, which reduce free radicals more efficiently than ascorbate. Phenolic hydroxyl groups are more stable because of the resonance of aromatic radical structures [231]. Additionally, polyphenols have low reduction potentials, such that the oxidized form of a given target molecule is more likely to be reduced by receiving an electron. In other words, polyphenols tend to donate electrons to biologically relevant radicals, which have higher standard reduction potentials. The stability of the newly formed radical polyphenol determines its structural requirements. One requirement is that moieties that maximize flavonoid antioxidant potential include a catechol group, a 2,3-double bond conjugation with a 4-oxogroup, and 3- and 5-hydroxyl groups. These required groups all mediate stable electron delocalization [216, 218, 231]. Moreover, there is a positive correlation between the number of hydroxyl groups and the antioxidant potential of a polyphenol.

Polyphenols interact with the Aβ-metal complex

The well-known therapeutic effect of polyphenols in fibril disaggregation may stem from polyphenol hydrophobic nature and metal chelation activity. The bifunctionality of polyphenols, specifically metal chelation activity and Aβ interaction, forms a ternary complex between the $A\beta_{42}$ peptide, metal ion, and polyphenol, which further decreases the toxicity of the metal-Aβ species, in addition to antioxidant effects (Fig. 8) [42, 207, 211]. Characterization of the complex formed by curcumin and two truncated $A\beta_{42}$ segments using mass spectrometry and spectroscopic techniques showed that curcumin partially chelates Cu(II) from the $A\beta_{6–14}$ binding site, despite of the strong His interactions [232]. This result suggests that curcumin is a potential metal redistributor. Moreover, the interactions between Cu(II), curcumin, and $A\beta_{14–23}$ peptide show a stable ternary complex, indicating that the polyphenol simultaneously acts as a chelator and direct interactor with the $A\beta_{42}$ peptide. Picciano and Vaden demonstrated the bifunctionality of curcumin. Further,

molecular models show that $A\beta_{42}$ peptide conformational changes are essential for oligomerization and these changes are affected by Cu(II) and curcumin [139, 152, 233, 234]. When curcumin is included in these models, curcumin reduces β-sheet conformation and increases stability of an α-helical structure, and the α-helical structure stabilizes monomeric forms [234]. These models indicate the possibility of an Aβ-Cu(II)-curcumin ternary complex, making curcumin a double-action $A\beta_{42}$ aggregation inhibitor, via metal chelation activity and direct interaction with $A\beta_{42}$ peptide. With EGCG, nuclear magnetic resonance (NMR) and mass spectrometry studies of Aβ-Cu/Zn(II)-EGCG ternary complexes suggested that metal chelation, $A\beta_{42}$ interactions, and ternary complex formation occur in parallel [207]. There is also evidence that flavonols, such as quercetin and myricetin, form Aβ-metal-flavonol ternary complexes via hydrophilic interactions between the hydroxyl groups and the $A\beta_{42}$ peptide [211].

Based on the existing body of knowledge, we propose that the stability of Aβ-metal-polyphenolternary complex arises from metal oxophilicity and the “hardness” of the groups that determinethe potential metal binding in the polyphenol. Additionally, stereoelectronic effects and resulting five- or six-membered rings increase the stability of the Aβ-metal-polyphenol ternary complex. Moreover, $\pi - \pi$ stacking between polyphenol phenolic rings and $A\beta_{42}$ peptide aromatic aa residues destabilize β-sheet structures [235]. Overall, the therapeutic effects of polyphenols decrease neurotoxicity caused by $A\beta_{42}$ peptide and dysregulated metals.

In Fig. 9, we propose a mechanism by which polyphenols act as chelator molecules. AβPP and $A\beta_{42}$ are considered metalloproteins because both have a metal binding site. Polyphenols can interact directly with metal transition ions and also interact with the Aβ-M complex. We suggest that polyphenols are neuroprotective, and should be studied as natural chelator molecules for regulating metal transition ion imbalance in the brain.

Polyphenols as potential drug for the treatment of Alzheimer’s disease

We strongly advocate that polyphenols have potential to be a new drug against AD and others neurodegenerative disorders. Polyphenols have also been considering nutraceutical compounds with the advantage to be taken as dietary supplement in any stage of illness. Notably, five drugs have been approved by Food and Drug Administration (FDA) for treatment of AD: these are donepezil, galantamine, rivastigmine, memantine, and the combination of donepezil with memantine, all with limited short term benefits [236, 237]. We consider that polyphenols have the potential to be converted in a new drug in the fighting against AD. Curcumin, a well-known polyphenol, has similarity with donepezil (Fig. 10) where both have two aromatic rings and they are connected with a chain that contain keto group. There are synthetic compounds that took the half part of each compound and created a novel molecule with major potential than their precursor such as donepezil and curcumin [238]. The disadvantage of curcumin is the low bioavailability and its degradation in the organism. If we improve the bioavailability and avoid the degradation of this polyphenol, it can be converted to a new drug against AD.

CONCLUSIONS

Polyphenols have high therapeutic potential because they are natural chelators that can cross the BBB. These biomolecules reduce metal accumulation by forming one or more stable 5- or 6-membered rings. The chelation activity of polyphenols avoids metal imbalance, prevents ROS production, and disturbs Aβ fibril patterns. The chelation potential of polyphenols may be related to their anti-amyloidogenic properties that allow for the formation of ternary complexes between Aβ, metal ions, and the polyphenol. We propose that the chelation potential and antioxidant properties of polyphenols make these biomolecules strong pleiotropic candidates for chelation therapy compounds. We also consider that polyphenols have therapeutic potential for AD. Polyphenols are a natural product that can interact with transition metal ions and the Aβ-metal complex.

ACKNOWLEDGMENTS

The authors acknowledge research fundings by: National Secretariat for Science, Technology, and Innovation of Panama (SENACYT) grant number [FID17-002], INDICASAT Internal Grant [JR04-2020] to KSR and National Institute of Neurological Disorders and Stroke (NINDS) of the National Institute of Health (NIH) grant R01NS088645 to MLH. The content is solely the responsibility of the authors and does not necessarily represent the official views of the funding agencies.

J.L-B., and K.S.R. are grateful to Melo Brain's Grant, MEF Nutritional Grant for support and INDICASAT Internal Grant. JL-B. and K.S.R. also thank the National Science System (SNI) of National Secretariat for Science, Technology, and Innovation of Panama (SENACYT) for support. GLP is grateful to INDICASAT for financial support of the collaboration.

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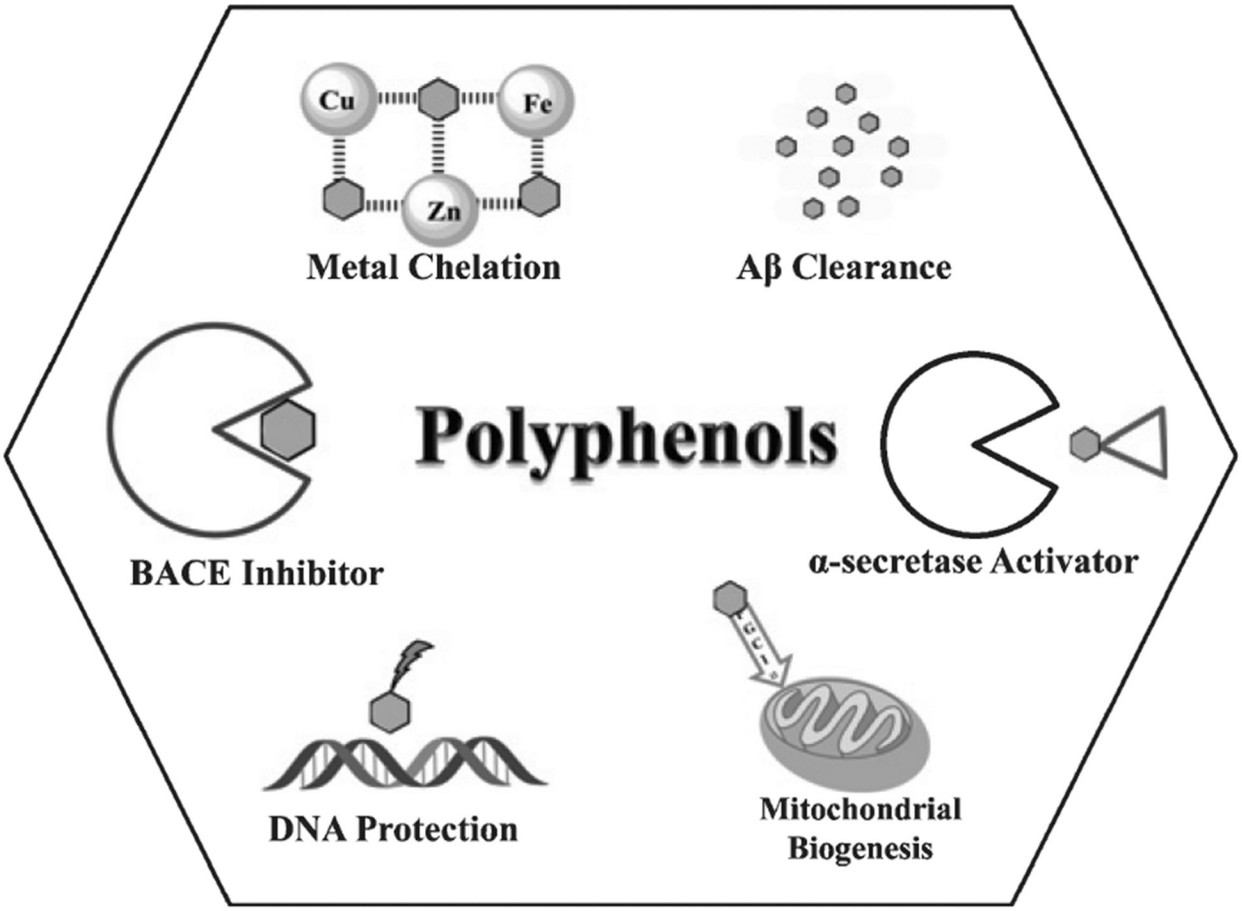

Fig. 1.

Potential therapeutic effects of polyphenols. Metal chelation occurs via coordination with oxophilic transition metals, such as Cu, Zn, and Fe, which are abundant in the CNS. Transition metals can induce ROS, which damage the genome. Therefore, polyphenols have DNA protection activity. Polyphenols modulate the AβPP pathway in two different ways. One pathway activates α-secretase by removing the pro-domain, which induces the non-amyloidogenic pathway. A second pathway favors neuroprotection, wherein polyphenols inhibit the β-site amyloid protein precursor cleaving enzyme 1 (BACE1), leading to decreased Aβ concentration. Polyphenols also promote Aβ clearance through non-covalent interactions with amino acid residues that disrupt Aβ structure stability, thus leading to fibril disaggregation. Polyphenols can also induce mitochondrial biogenesis by stimulating PGC-1α.

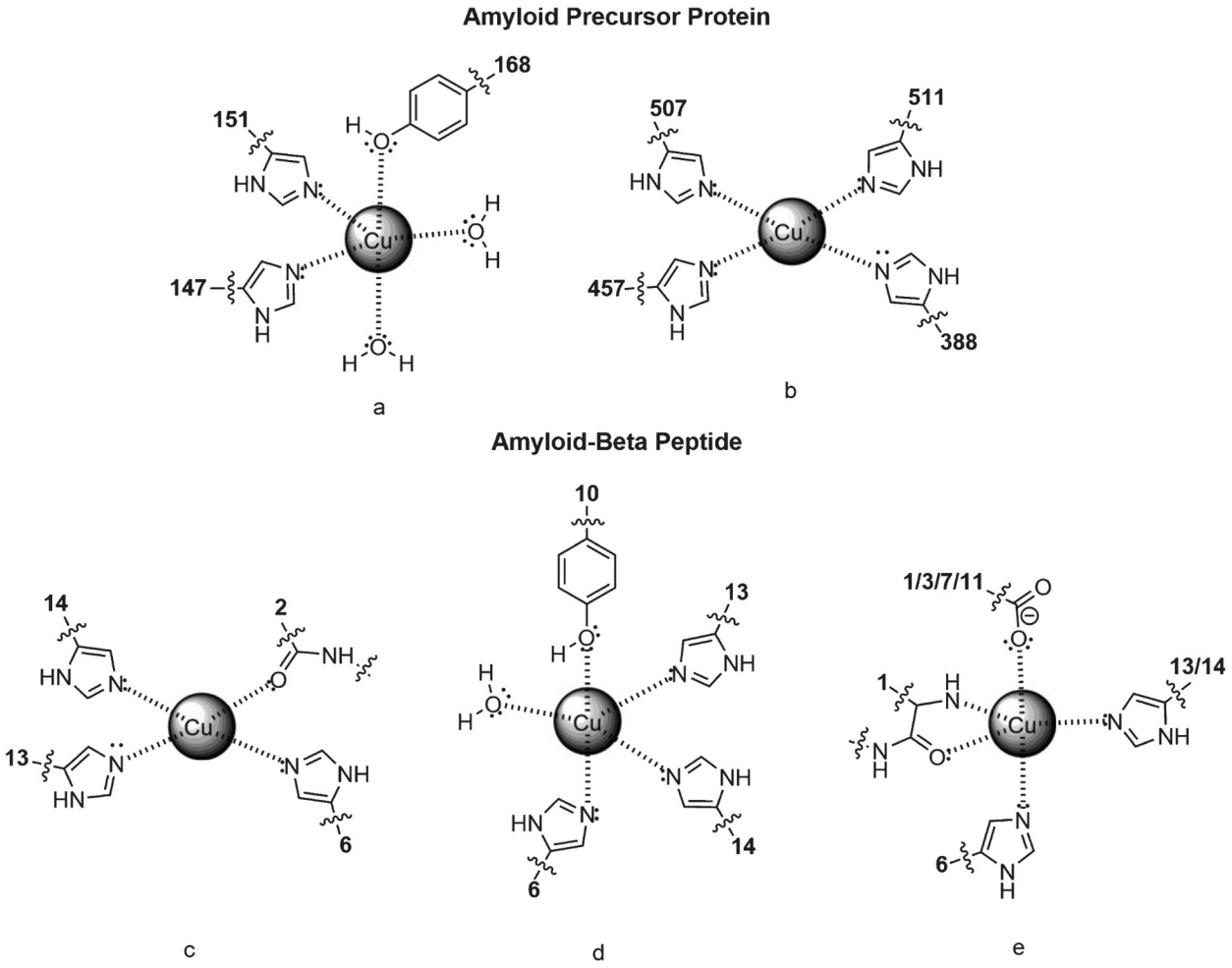

Fig. 2.

Cu binding interactions with AβPP and $A\beta_{42}$. a) Configuration of Cu with residues His147, His151, Tyr168 in APP's copper binding region and two water molecules in a trigonal bipyramidal geometry. b) Configuration of Cu with residues His388, His457, His507, and His511 in APP E2 domain. c) Cu binding with $A\beta_{42}$ residues Ala2, His6, His13, and His14 in a tetrahedral square planar configuration. d) Cu binding to $A\beta_{42}$ residues His6, Tyr10, His13, His14, and a water molecule in a trigonal bipyramidal configuration. e) Square-base pyramidal arrangement of Cu with $A\beta_{42}$ residues Asp1, His6, His 13 or 14, and the carboxylate of Asp1, Glu3, Asp7, or Glu11.

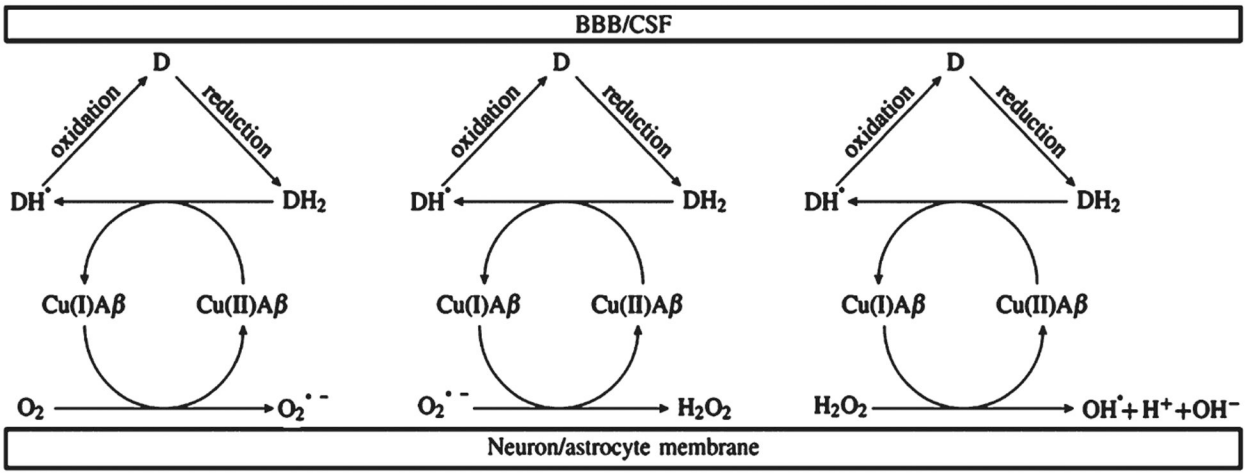

Fig. 3.

One-electron transfer cycle during ROS production within the synaptic cleft. DH_2 is ascorbic acid and D is dehydroascorbic acid. The blood-brain barrier (BBB) is in contact with cerebrospinal fluid (CSF).

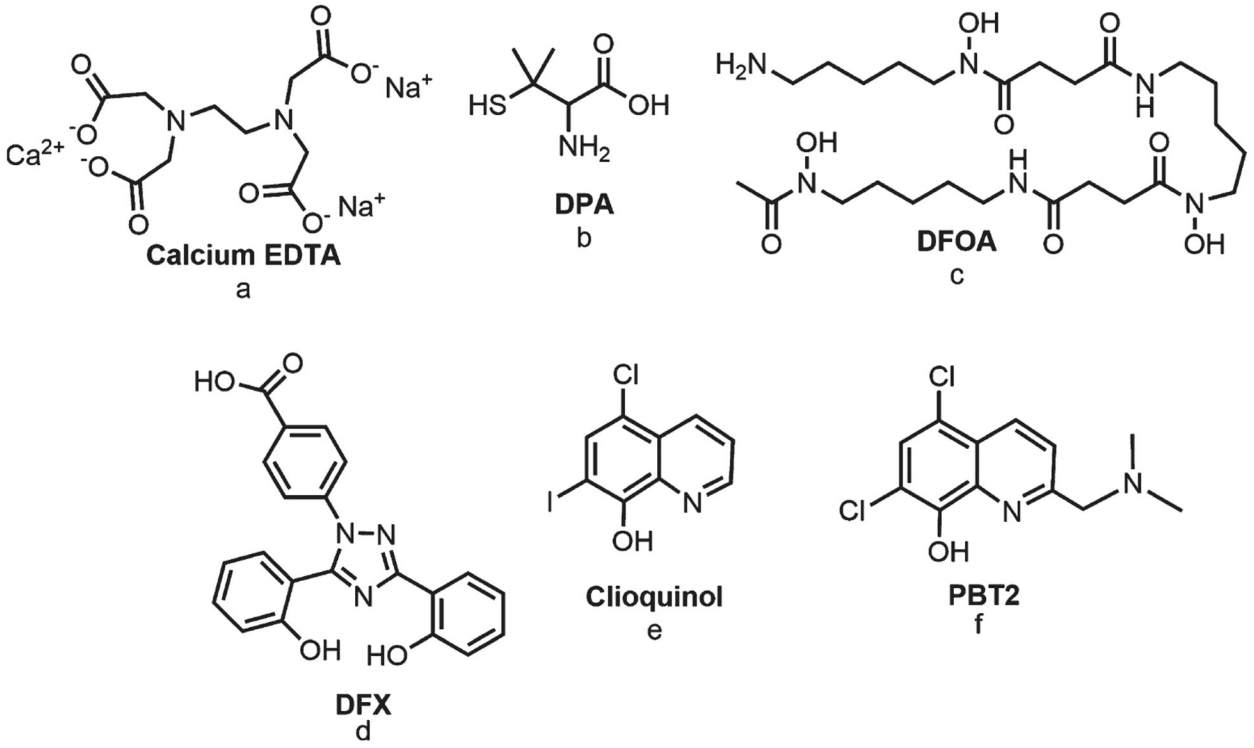

Fig. 4.

Types of metal chelation compounds. Compounds a–d are approved for treating metal ion excess. Compounds e–f are considered metal-protein attenuating compounds (MPAC).

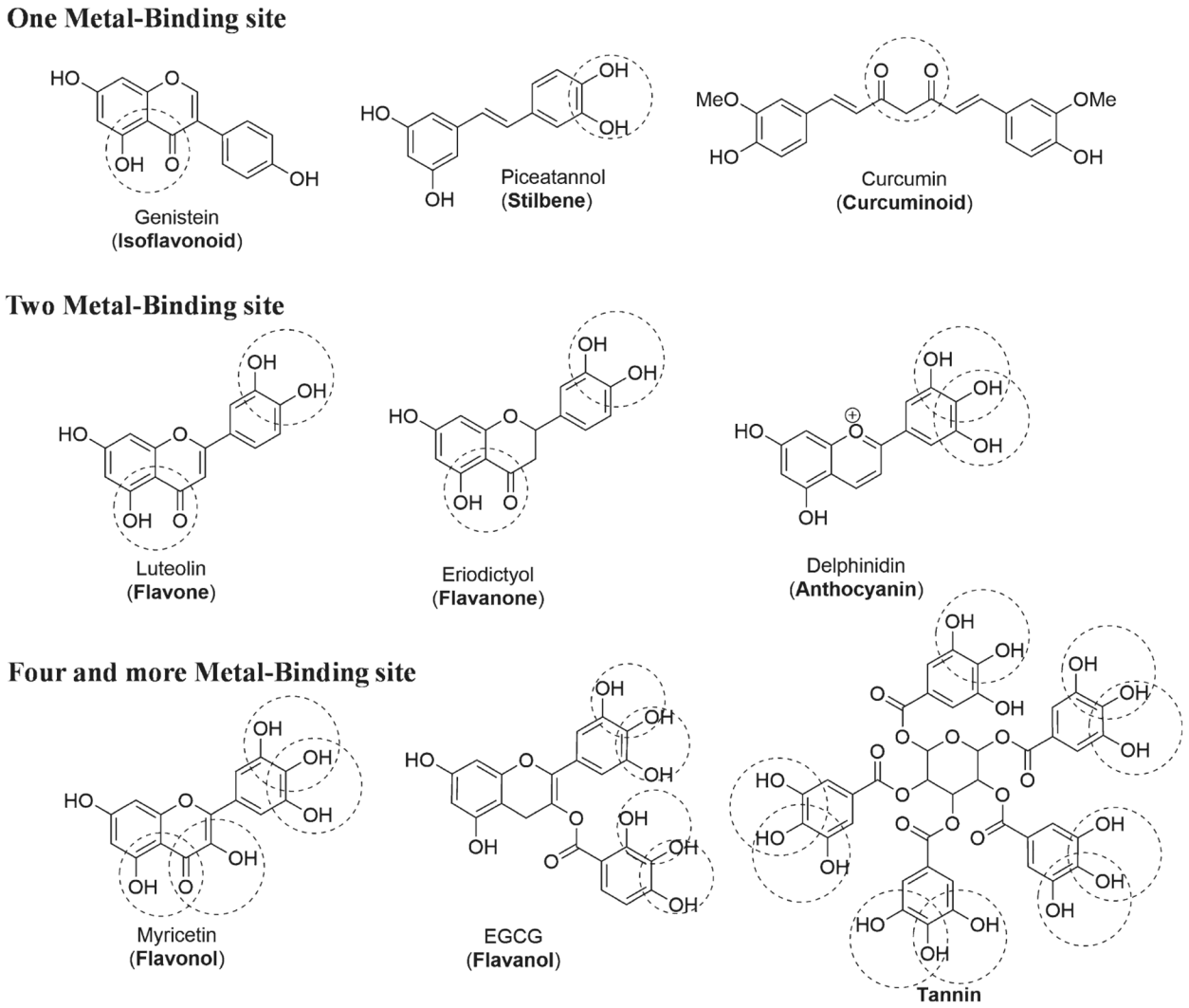

Fig. 5.

Classification of polyphenols according to the number of metal binding sites (common names in parenthesis).

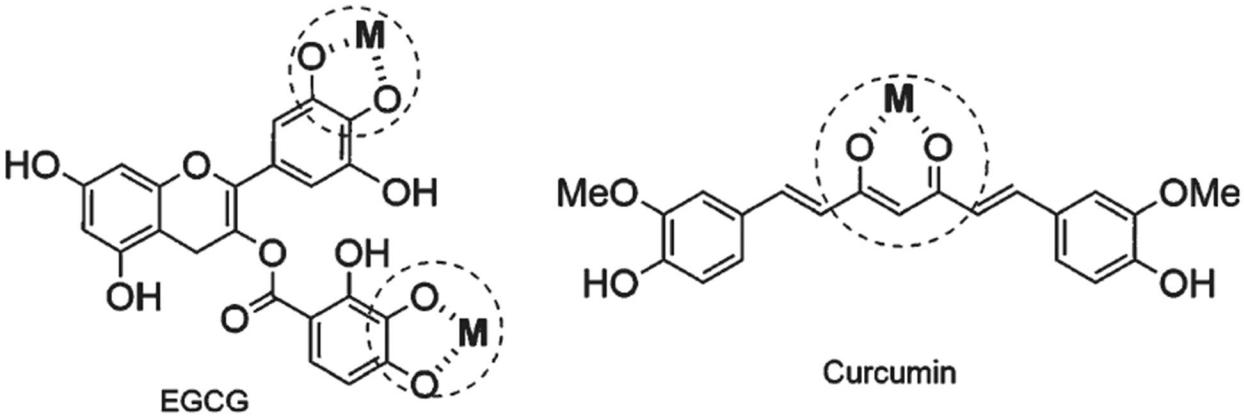

Fig. 6.

Polyphenols interact with transition metal ions to form a stable 5- membered ring as EGCG or 6-membered ring as curcumin.

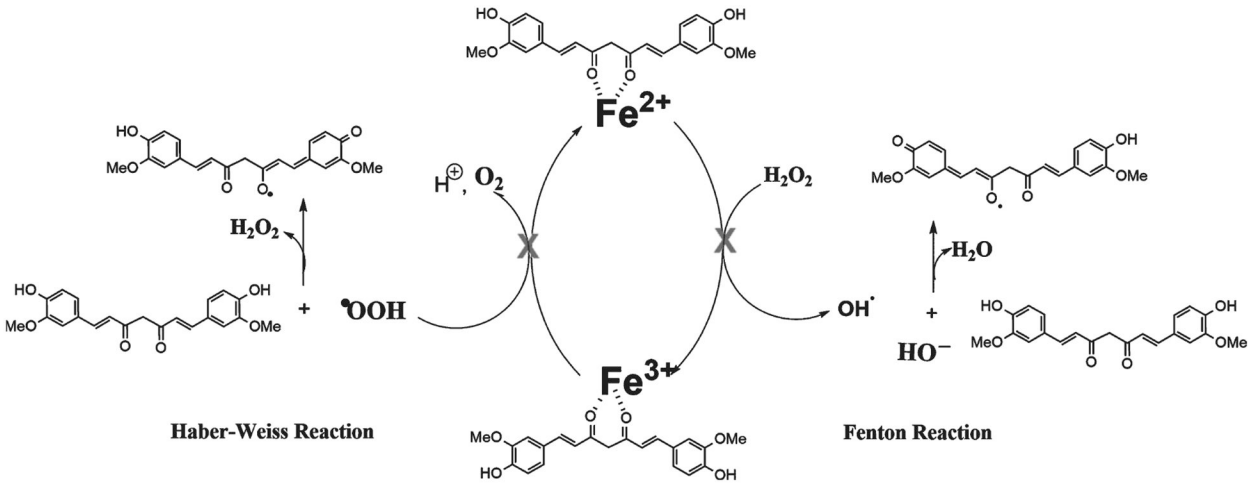

Fig. 7.
Polyphenols interact with transition metal ions and avoid Haber-Weiss and Fenton reactions.

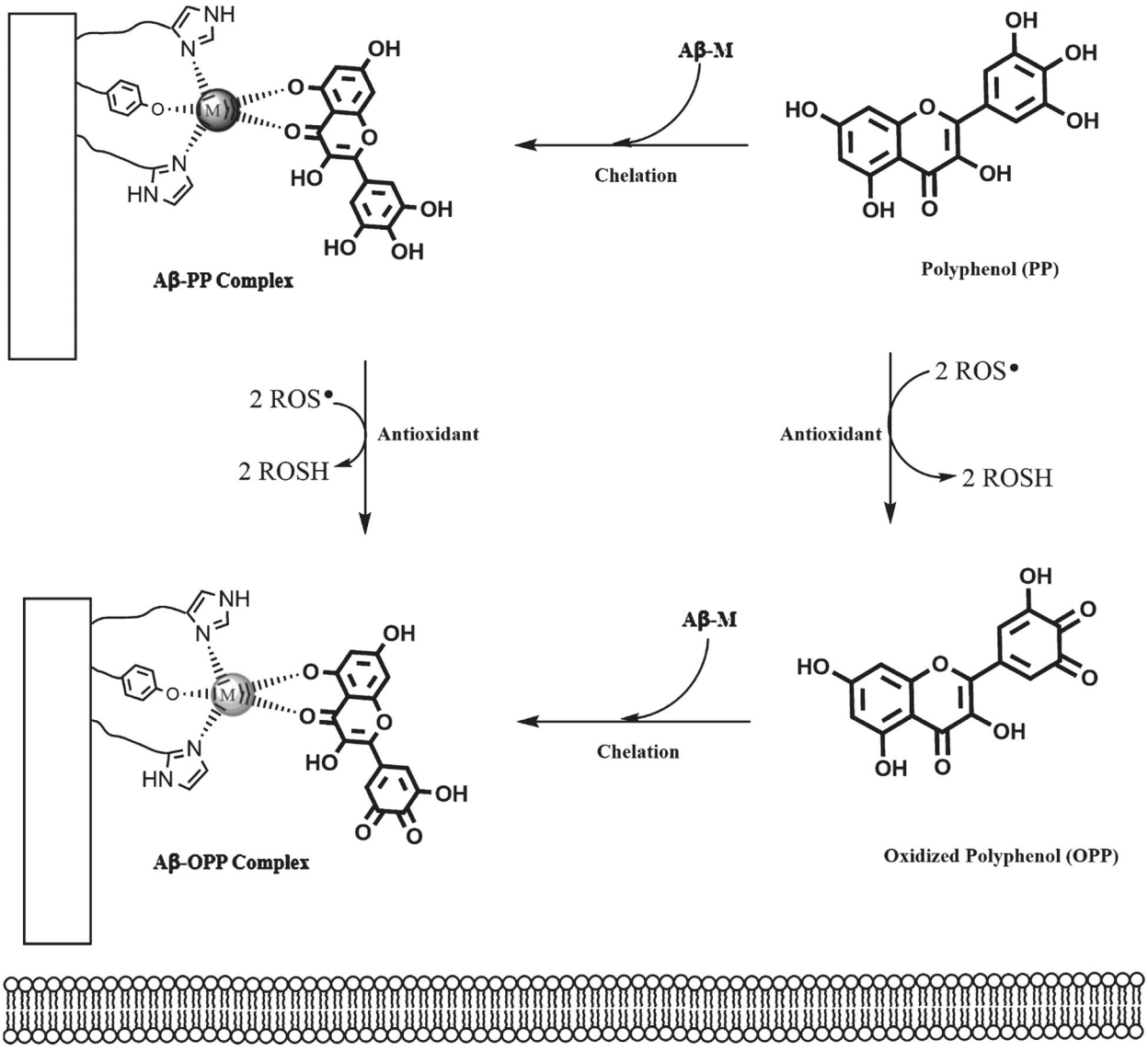

Fig. 8.

Bifunctionality of polyphenols, which form an Aβ-M-PP ternary complex and also interact with ROS.

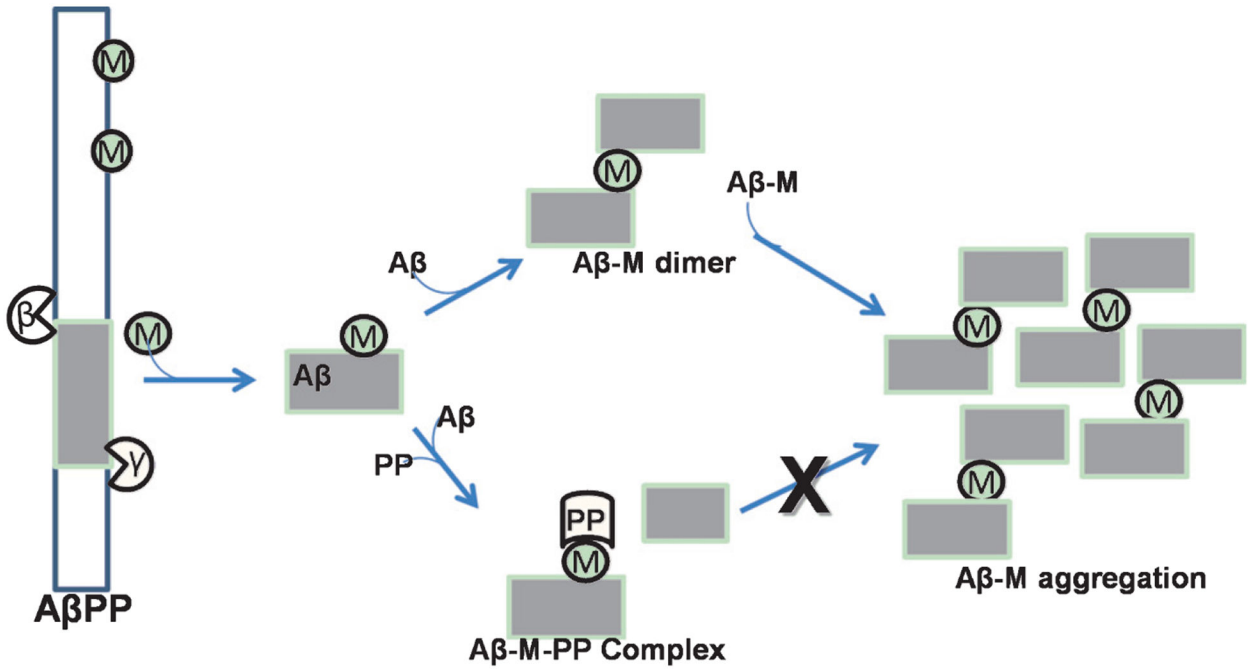

Fig. 9.

Potential mechanism of polyphenol neuroprotection caused by the ternary complex Aβ-M-PP, which may prevent Aβ-M aggregation.

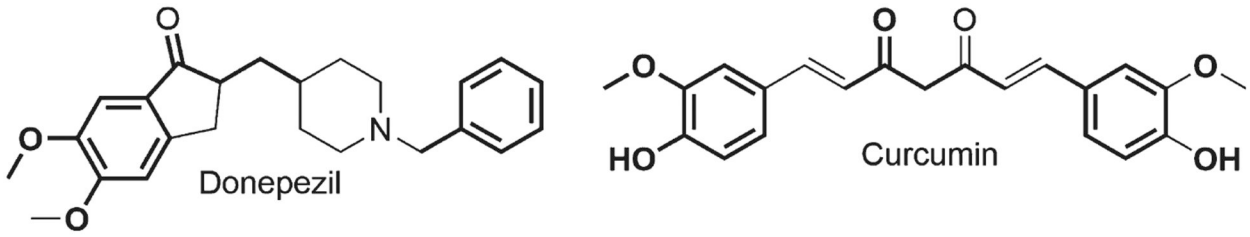

Fig. 10.
Structural comparison between donepezil and curcumin.