Al-Rafidain J. Med Sci. 2021;1:53-61.
doi: 10.54133/ajms.v1i.31
Review Article

AJMS
Online ISSN (2789-3219)

The Role of Polyphenols in the Treatment of Alzheimer's Disease: Curcumin as a Prototype

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Received: September 2021; Revised: September 2021; Accepted: October 2021

Abstract

Many epidemiological studies suggest a polyphenol-rich diet can help prevent Alzheimer's disease (AD), and examined the effects of various natural polyphenols on amyloid-protein (Aβ) aggregation using well-known *in vitro* and *in vivo* models of cerebral amyloidosis. *In vitro* studies showed that these polyphenols reduce Aβ oligomer-induced synaptic and neuronal toxicity by preventing Aβ oligomerization and fibril formation. Furthermore, polyphenolic compounds reduced soluble Aβ oligomers and insoluble A deposits in the brain of transgenic mice fed orally. According to a new review of the literature, natural polyphenols have anti-amyloidogenic effects on Aβ, in addition to anti-oxidant and anti-inflammatory properties. Well-designed clinical trials or polyphenol-based preventive treatments are required to prove polyphenols' disease-modifying efficacy.

***Keywords**:* Alzheimer's disease, polyphenols, beta amyloid, mechanisms of action

دور البوليفينولات في علاج مرض الزهايمر: الكركمين كنموذج أولي

الخلاصة

تشير العديد من الدراسات الوبائية إلى أن اتباع نظام غذائي غني بالبوليفينول يمكن أن يساعد في الوقاية من مرض الزهايمر، وبينت تأثير البوليفينولات الطبيعية المختلفة على تكوين بروتين الأميلويد باستخدام نماذج معروفة في المختبر وفي الجسم الحي من الداء النشواني الدماغي. وأظهرت الدراسات أن البوليفينولات تحد من تسمم الخلايا العصبية عن طريق منع أتكوين وتشكيل الفيبريل. وعلاوة على ذلك، خفضت مركبات البوليفينول أوليغومرات الأميلويد القابلة للذوبان ورواسب بروتين الأميلويد غير القابلة للذوبان في ادمغة الفئران المعدلة وراثيا. وفقا لاستعراض جديد للأدبيات، للبوليفينولات الطبيعية فعالية مضادة لتكوين الأميلويد، بالإضافة إلى خصائص مضادة للأكسدة والالتهابات. هناك حاجة لتجارب سريرية مصممة جيدا أو علاجات وقائية قائمة على استخدام البوليفينولات لإثبات فعاليتها ضد مرض الزهايمر.

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Article citation: Alattiya RH, Tarish FK, Hashim LL, Hussain SA. The role of polyphenols in the treatment of Alzheimer's disease: Curcumin as a prototype. *Al-Rafidain J Med Sci.* 2021;1:53-61. doi: 10.54133/ajms.v1i.31

INTRODUCTION AND DEFINITIONS

Alzheimer's disease (AD) is a progressive neurodegenerative disease of the central nervous system. Alois Alzheimer defined AD in 1906. Alzheimer's disease affects over 5.2 million Americans, with the number expected to rise to 114 million by 2050 [1,2]. Alzheimer's disease has many known causes, but many more remain unknown. Regardless, it may have started spontaneously or be linked to a genetic mutation [3]. For example, mutations in genes coding for amyloid precursor protein (APP, chromosome 21), presenilin-1, and presenilin-2, all of which serve as targets for amyloid formation [4]. The apoprotein-E gene (ApoE gene) on chromosome 19 has the e4 allele in 25% of AD patients [5,6]. Alzheimer's disease is the most common cause of dementia, and the number of cases has risen significantly [7]. The condition also has a significant emotional and financial impact on patients, their families, and the community [8,9]. Memory, ability to perform and control daily functions, social functions, and poor emotional control are all impaired in AD-associated dementia, which is accompanied by a marked reduction in consciousness [10,11]. Degradation of synaptic connections and neuronal death in the forebrain and hippocampal regions of AD leads to memory loss while overall health is preserved [12,13]. These include early-onset AD (1-6%), which manifests between 30 and 60 years of age, and late-onset AD (90%) [14]. Thanks to advances in the discovery and characterization of highly sensitive biomarkers, it is now possible to distinguish between AD and AD associated dementia, allowing for more precise diagnosis and treatment [15]. Until recently, the origins of AD were unknown, and many of the components involved were considered scientific mysteries. In many AD-associated illnesses, there is a close association between genetic abnormalities and amyloid (A) accumulation, indicating that A accumulation is a critical factor in AD [16,17]. Excessive consumption of high-calorie Western foods may contribute to insulin resistance, cerebrovascular damage, mitochondrial dysfunction, and chronic inflammatory diseases [18,19]. These variables may cause A and Tau protein denaturation and hyperphosphorylation in brain tissue [20]. It is unknown how this protein contributes to higher levels of A. Several mechanisms have been proposed to explain AD etiology.

MECHANISMS AND ETIOLOGY

The amyloid cascade

Amyloid-β precursor protein (APP) proteolysis and APP cleavage by α-, β-, and γ-secretases form amyloid-β. The α-secretase-catabolized APP becomes a soluble form fragment (sAPP-α), which is involved in various physiological processes [21]. A (40 and 42) is synthesized by A (40 and 42) after sAPP is cleaved by β-secretase into sAPP and a 99 amino acid membrane bound fraction (nc99) [22]. That patients benefit from the use of inhibitors of secretase and a boost in secretase activity is hypothesized. The imbalance of A production and elimination by Neprilysin and angiotensin converting enzyme (ACE) causes amyloid accumulation and senile plaque formation [23,24]. Because these enzymes have diverse substrates, using α- and γ-secretase inhibitors may result in increased α-secretase and decreased Aβ accumulation, but also significant side effects [25]. Less side effects are associated with selective secretase inhibitors [26]. Another mechanism targets amyloid aggregate clearance and deposition by activating enzymes like Neprilysin, IDE, plasmin, endothelin converting enzyme, ACE, and MMTPs. However, enzyme levels and activity fluctuate over time [27,28]. Amyloid can also be trapped in the peripheral circulation to improve the flow of amyloid from the CNS to the peripheral circulation [29]. Another method focuses on τ-proteins, which help stabilize microtubule filaments [30]. The hyperphosphorylation of these proteins causes neurofibrillary tangles (paired helical filaments; PHF). Decreased microtubule binding leads to cytoskeleton instability and neurodegeneration [31]. τ-protein inhibitors, microtubule stabilizers, and anti-immunotherapy have all been shown to improve protein clearance [32].

Cholinergic theory

In the cholinergic hypothesis, cholinergic neurons in the cerebral cortex and hippocampus are lost, along with choline acetyltransferase, Ach release, and nicotinic/muscarinic receptors [33]. Giving Alzheimer's patients acetylcholine esterase inhibitors increases synaptic availability of Ach [34].

The dendritic hypothesis

Alzheimer's disease has reduced dendritic complexity and dendrite spin, according to this theory. Some studies claim that amyloid-oligomers are neurotoxic, and that their interaction with prion protein activates NMDA receptors [16]. Alzheimer's disease is classified as sporadic (95%) or non-sporadic (5 percent). In the late-onset sporadic form of AD, the prevalence of AD doubles every 5 years after the age of 65 [35]. Mild, moderate, and severe are the three primary stages of the disease. Alzheimer's disease is characterized by amyloid plaque, neurofibrillary tangles, glial response, and prolonged synaptic and neuronal loss [36].

TARGETS FOR AD TREATMENT

The pathogenesis of AD involves the formation of neurofibrillary tangles and the extracellular accumulation of Aβ. Treatments based on the amyloid cascade hypothesis and others involving τ-proteins are being pursued [37].

Beta and gamma secretase inhibition

β-secretase selectively cleaves APP, the major precursor of Aβ, into sAPP and a 99 amino acid membrane bound fragment (C99). Additional secretase processing of the C99 fragment results in Aβ(1-40) or Aβ(1-42), peptides involved in senile plaque formation [21,22]. Targeting the secretase enzyme is difficult due to the complex's diverse substrates. As a result, inhibiting this enzyme may have a variety of negative effects. However, clinical studies on E2609 have shown that it can reduce Aβ production in the CSF by up to 90%. No commercial β-secretase inhibitors exist [38,39]. Another inhibitory strategy involves blocking the γ-secretase complex. This method, like β-secretase inhibition, has many drawbacks due to interference with other routes and substrates. One such substrate is the notch protein, which regulates cell growth,

differentiation, and communication [40]. Inhibitors of γ-secretase, such as Semagacestat and Avagacestat, have not been approved for marketing because the former caused significant adverse reactions such as cognitive decline and decreased ability to perform daily activities, and the latter was ineffective [41]. To avoid the negative effects of overall enzyme inhibition, selective γ-secretase modulators (SGSM) could be developed [42].

Inhibition of Aβ aggregation

The accumulation of amyloid plaques, extracellular deposits of Aβ protein, both diffuse plaques of amorphous, primarily nonfibrillar Aβ aggregates and neurotic plaques of fibrillar Aβ arranged in a β-pleated conformation [43]. Plaque-preventing substances have been developed. Only 3-amino-1-propaneosulfonic acid (3-APS, Alzhemed, tramiprosate) has reached phase III studies [44]. This compound was created to prevent Aβ from interacting with glycosaminoglycans, which have been linked to Aβ plaque formation [44]. Despite its potential, this drug was halted in Europe in 2007 due to negative phase III clinical trial results [45]. Two other 8-hydroxyquinolones, clioquinol and PBT2, have also been studied in humans [46]. They are thought to work by preventing the base metals from interacting with the Aβ brain peptide. The reason for this therapy target is that copper ion binding to Aβ leads to the formation of reactive oxygen species [47,48]. These drugs failed phase II and III clinical trials due to ineffectiveness.

Removal of amyloid aggregates

Eliminating Aβ aggregate plaques is another promising AD treatment method. This is accomplished through the use of enzyme pathways, Aβ transit between the brain and the peripheral circulation, and immunotherapy, as described below:

Activation of enzymes that degrade amyloid plaques

Proteases that break down amyloid plaques and aggregates include neprilysin, IDE, plasmin, endothelin converting enzyme, angiotensin converting enzyme, and metalloproteinases [49]. Because these enzymes are non-selective, no drug has ever reached clinical trials.

Transit modulation between CNS and peripheral circulation

The transport of Aβ between the brain and the peripheral circulation is regulated by three molecules: 1) apolipoproteins, which transport Aβ from the blood to the brain; 2) low density lipoprotein receptor related protein (LRP-1), which increases Aβ outflow from the brain to the blood; and 3) receptor for advanced glycation end product (RAGE), which transports Aβ across the BBB [50-52]. Inhibition of apolipoproteins, peripheral administration of (LRP-1) or blocking RAGE reduces cerebral Aβ levels. The most common method is to deliver LRP-1 via peripheral nerves [53]. RAGE inhibitor/modulator PF-0449470052, which failed in phase II studies, and TTP4000, which finished its phase I trial in February 2013, are the only clinical candidates (NCT01548430). The trial's findings are still secret [54,37].

Anti-amyloid immune therapy

Aβ(1-42) (the predominant form found in senile plaques) or other synthetic fragments have been tested in transgenic AD mice. Both passive and active Aβ-specific antibodies have been tested in AD transgenic mice [55]. Active immunization tests work by activating the microglia's phagocytic function. On injected a QS-21 adjuvant with a synthetic full-length Aβ (1-42) peptide (AN1792). Despite promising human studies, (AN1792) caused significant side effects, halting phase II trials due to aseptic meningoencephalitis [56]. Second generation vaccines use a shortened Aβ(1-6) peptide region to avoid nonspecific immune responses. Novartis' CAD106 is the first second-generation vaccine to enter trials. A recent phase II clinical trial of CAD106 showed a 75% Aβ specific antibody response without severe inflammatory reactions. Among the other vaccines in development are ACI-24, MER5101, and AF205 [57]. Bapineuzumab and solanezumab are humanized monoclonal antibodies against Aβ(1-6) and Aβ(12-28) [58,59]. Bapineuzumab reduces amyloid plaques in the brain and phosphorylated tau in the CSF. Despite this, the medication had no effect on cognitive function. However, solanezumab has been shown to improve cognitive function in mild AD [59]. Gantenerumab is another monoclonal antibody being studied in people at risk of developing pre-senile AD due to genetic abnormalities [60]. It's a highly specific IgG1 antibody designed to bind to a structural epitope on amyloid fibers. This will activate microglia, which will phagocytose amyloid plaques. Studies on transgenic mice back this up [61].

STRATEGIES BASED ON TAU PROTEINS

Tau proteins are abundant in neurons and play a significant role in microtubule stability, especially in axons. In AD, tau-protein is hyperphosphorylated, resulting in the production of insoluble paired helical filaments (PHF) and neurofibrillary tangles. This will result in cytoskeleton instability, neurodegeneration and neuronal death [62]. More research is needed to better understand the particular molecular pathways involved in Tau neurotoxicity. According to recent study evaluating the neurotoxic properties of various forms of τ-proteins, the soluble form is the most dangerous [63]. This is supported by a recent investigation that identified oligomeric τ-proteins as dangerous [64]. As a result, future therapeutic strategies should focus on τ-protein variations that are soluble. Tau-based methods include inhibiting τ-protein phosphorylation, blocking its aggregation, microtubule stabilization, and anti-τ-protein immunotherapy. Phosphorylation of τ-proteins affects their interaction to microtubules. Under normal circumstances, the protein stays soluble, but pathological hyperphosphorylation of a τ-protein impairs its normal function [65]. Hyperphosphorylation is caused by an imbalance in the catalytic activity of kinases and phosphatases. CDK5, GSK3, Fyn, JNK and p38 stress-activated protein kinases, and mitogen-activated protein kinases ERK1 and ERK2 mitogen-activated protein kinases have all been reported to have elevated expression in the areas proximal to neurofibrillary tangles in AD [66]. Kinase inhibition is a natural target for re-establishing the balance

between kinases and phosphatases. In an APP/PS1 transgenic mice model of AD, SP600125, a popular pan-JNK inhibitor, improves cognition and slows neurodegeneration [67]. Tau-proteins that have been hyperphosphorylated cluster together to form neurofibrillary tangles, which help AD progression. The use of methylene blue dye molecules to prevent τ-protein aggregation has showed potential. Methylene blue disrupts τ-proteins aggregation, inhibits amyloid aggregation, improves mitochondrial electron transport chain efficiency, reduces oxidative stress, prevents mitochondrial damage, and modulates autophagy. A first-generation medicine produced from methylene blue (Rember) appears to decrease the progression of AD in a 50-week clinical trial. TRx 023, a pure derivative of methylene blue with the dual action of preventing and dissolving τ-protein clumps, was developed as a result of this progress [66]. Tau-proteins are required for microtubule stabilization, as previously established. As a result, microtubule stabilizers may compensate for non-functional hyperphosphorylated τ-protein activity and provide effects similar to τ-protein hyperphosphorylation and aggregation inhibitors. Paclitaxel is a microtubule stabilizer used in oncology, but its inability to cross the blood-brain barrier and significant adverse effects prevent it from being employed in AD treatment [68]. Epothilone D is a microtubule-stabilizing medication that improves axonal transport, lowers axonal dystrophy, reduces τ-protein neuropathology, and slows the loss of hippocampal neurons. Despite this, after a failed clinical trial in 2013, development was discontinued [69]. Active and passive immunotherapies have both been shown to minimize τ-proteins aggregation and boost clearance of τ-protein oligomers and insoluble aggregates. Monoclonal antibodies directed against hyperphosphorylated τ-proteins improved cognition in rats without causing any significant negative effects [70]. AADvac-1 is an active immunotherapy candidate that is now being investigated in a phase I trial to see if it is safe and tolerable. A synthetic peptide derived from the τ-protein sequence and keyhole limpet hemocyanin make up the antigen. The exact molecular composition of the antigen has yet to be determined (NCT01850238 and NCT02031198) [71].

NATURAL POLYPHENOLS AS THERAPY IN AD

Hundreds of polyphenols have been demonstrated to successfully scavenge ROS and RNS and to protect against degenerative diseases associated with aging [72]. However, some of the evaluated anti-oxidant compositions did not demonstrate the expected positive results in clinical testing [73]. Because the molecular origins of degenerative diseases are complex and mostly unknown, developing therapeutics to combat them is difficult. Since ancient times, polyphenol-rich diets have been known to provide health benefits against aging-related illnesses. According to several research findings, natural compounds having multiple polyphenol groups may be more effective disease-fighting agents. *In vitro* experiments have indicated that polyphenol (e.g., tannins)-containing substances protect against AD [74]. Larger polyphenols, on the other hand, may have a decreased permeability of the blood-brain barrier. *In vivo*, the breakdown of these big molecules and their metabolites may act as a single polyphenol moiety [75]. Curcumin, ferulic acid, and styryl benzene all have individual phenolic groups that are potent antioxidants [76]. According to these studies, polyphenol groups comprising natural anti-oxidants may be better and more effective anti-oxidant molecules. Natural food ingredients may be the best currently available option because additional anti-oxidant compositions have not been proved to be useful in avoiding degenerative illnesses [77]. A wide variety of fruits and vegetables high in flavonoids and other polyphenols may be useful in delaying or reversing the multi-stage degenerative events linked to aging and oxidative stress, meaning that a healthy diet can help prevent disease. These polyphenols protect neurons from the damage induced by β-amyloid deposition by forming soluble and less toxic amorphous aggregates. In a mouse model of AD, a walnut-rich diet has been shown to improve memory, learning ability, and anxiety [78]. The National Health and Nutrition Examination Study [79] discovered a connection between walnut consumption and cognition scores in adults. Walnuts include antioxidants such as flavonoids, phenolic acid, melatonin, gamma tocopherol (vitamin E), selenium, and α-linolenic acid [80,81]. Walnuts inhibit ROS generation and oxidative stress, as well as plasma membrane rupture and DNA damage, despite the fact that the exact mechanism is uncertain [82].

CURCUMIN AS A PROTOTYPE

In general, a healthy diet rich in phenolic compounds may help to avoid the onset of AD [83]. A Mediterranean-style diet has been shown to reduce the risk of AD. A high proportion of plant foods and fish, a moderate amount of wine, and a low proportion of red meat characterize this diet. It has been discovered that eating a Mediterranean-style diet was linked to a lower risk of AD (hazard ratio of 0.60, compared to 0.91 in non-Mediterranean nations) [84]. Similarly, Ng *et al*. found that eating an Asian-style diet rich in soybean and turmeric, as well as eating a lot of seaweed, lowered the risk of AD [85]. Given AD's multifaceted etiology and complicated clinical pathways, it's realistic to expect that treatments focusing on a single causative or modifying component will have limited results. As a result, therapeutic agents with pleiotropic activity, which target several impaired processes, are gaining popularity [86]. Several substances can meet these requirements, with curcumin exhibiting strong anti-Aβ effects as well as significant anti-inflammatory and antioxidant capabilities [87]. Curcumin is a component of the Indian spice turmeric, and it is produced from the rhizome of the *Curcuma longa* plant, which is widely grown in South and Southeast Asia, particularly China and India [88]. The curcumin complex, which is made up of curcumin (77%), demethoxycurcumin (17%), and bisdemethoxycurcumin (17%), is known as commercial curcumin (3%). Turmeric and natural curcuminoids have been utilized in herbal therapy to treat respiratory problems, abdominal pain, sprains, and edema [89]. Research suggests that curcumin may play an important role in the treatment of AD, and that it is particularly effective as a health-promoting life-long nutraceutical as well as a multi-targeted medication [87].

Curcumin also enhances synaptic plasticity and neurogenesis in healthy-aged rats, which improves memory performance [90]. It may also boost docosahexaenoic acid production, which improves plasma membrane integrity and keeps mitochondrial and synaptic function in check [91]. Curcumin supplementation in healthy elderly people has been studied in several trials. Di Silvestro and colleagues revealed that a low dose of lipidated curcumin increased nitric oxide levels and decreased the soluble intercellular adhesion molecule in healthy middle-aged people, resulting in a variety of possible health advantages [92]. Both compounds are linked to the risk of cardiovascular disease. Curcumin also reduced the activity of alanine aminotransferase, a general sign of liver injury, and increased plasma myeloperoxidase, a measure of inflammation. Moreover, Cox *et al* found that supplementing with a solid lipid curcumin formulation (80 mg as Longvida®) enhanced cognitive performance, reduced fatigue, and reduced the negative effects of psychological stress on mood, potentially improving the quality of life for the aging population [93]. As a result, consuming curcumin in the diet may lower the risk of AD, improve cognitive performance, and delay or prevent the effects of aging and neurodegenerative illness.

Curcumin's effects on Aβ protein

One contemporary strategy for treating AD is anti-amyloid treatments, which involve lowering Aβ production, preventing Aβ aggregation, and increasing Aβ clearance. Curcumin lowers Aβ levels *in vitro* by blocking the formation of amyloid precursor proteins and lowering the development of the sole β-secretase enzyme, β-secretase 1 (BACE1) [94]. Dimethoxy-curcumin also demonstrated a powerful BACE-1 inhibitory effect *in vivo*, assisting in the repair of morphological and behavioral defects produced by amyloid precursor protein maturation and BACE1 overexpression, according to *in vivo* studies using a drosophila AD model. Other studies have looked at the molecular mechanism of curcumin's inhibition of BACE-1. Curcumin suppresses BACE-1 transcription by activating the Wnt/-catenin pathway, which binds to T-cell factor-4, a regulator of the BACE1 gene [95]. In a detailed structure-activity investigation, the coplanarity of two phenol rings, the length and rigidity of the linker, and the substitution conformation of the phenol rings were determined to contribute to curcumin's inhibitory potency [96]. Rao et al. also shown that curcumin binding to Aβ-aggregates produces significant amino acid modifications, resulting in a shift in equilibrium toward non-toxic Aβ aggregates [97]. Curcumin inhibits Aβ aggregation by chelating metal ions such as Cu^{+2}, Zn^{+2}, and Fe^{+3}, which are likely agonists of Aβ aggregation and oxidative stress, according to other theories [98]. Curcumin's activities are not limited to modifying Aβ production and aggregation; in fact, recent study has shown that curcumin has the ability to accelerate Aβ clearance. Curcumin increases autophagy and the production of lysosome-related proteins like heat shock proteins, LC3A/B-II, and beclin-1, which are all necessary for Aβ phagocytosis in neurons [99]. CNB-001, a curcumin derivative, also works as a 5-lipoxygenase inhibitor, increasing the PERK/eIF2/ATF4 arm of the unfolded protein response and speeding up the breakdown of Aβ aggregates [100]. These findings not only suggest that curcumin plays a role in the Aβ cascade, but they also point to a slew of additional AD targets, including Wnt/-catenin and the unfolded protein response proteins PERK/eIF2/ATF4.

Anti-inflammatory properties

Neuro-inflammation is one of the pathogenic components in the vicious loop of AD pathogenesis, and it is characterized by high glial activation and potent cytokine production at the site of injury. Curcumin inhibits arachidonic acid synthesis and metabolism, pattern recognition receptor pathways on glial cell surfaces, and nuclear transcription factors, among other inflammatory signaling pathways [101]. It inhibits phospholipase-A2, cyclooxygenase-2, lipoxygenase, and microsomal prostaglandin E synthase-1, all of which are inflammatory enzymes [102]. Curcumin also inhibits toll-like receptor-4 dimerization, and lowers pro-inflammatory cytokines significantly [103]. Curcumin inhibits inflammasome activation of the nucleotide-binding oligomerization domain (NOD)-like receptor protein-3 (NLRP3), which appears to lessen neurotoxicity and the inflammatory response associated with it [104].

Anti-oxidant properties

As previously indicated, Aβ and phosphorylated τ-protein aggregation, inflammation, and oxidative stress all have a role in AD-associated neuronal death and cognitive impairment. As a result, anti-oxidant medicines have been recommended as a new approach for AD prevention and treatment. Curcumin has significant antioxidant benefits in mice and humans [105], increasing superoxide dismutase and catalase activity, maintaining reduced glutathione levels, and lowering malonyldialdehyde (MDA) accumulation. According to a study using a homocysteine-induced rat aging model [106], curcumin improves learning and memory function by substantially reducing MDA and super oxide anion levels in the hippocampus. Curcumin also reduces oxidative stress and cell toxicity caused by Aβ, both of which are telomerase-dependent. Telomerase is a ribonuclear protein complex that synthesizes and elongates telomeric DNA to protect cells against senescence [107]. These findings suggest that telomerase is a unique target of curcumin, perhaps paving the way for a new AD treatment.

Conclusion

Polyphenol-rich diets (red wine, green tea, etc.) have been related to a lower incidence of AD in numerous epidemiological studies. According to experimental studies, natural polyphenols have distinct effects on pathways involved in the pathophysiology of cerebral amyloidosis, such as modulation of APP processing, inhibition of Aβ aggregation and destabilization of aggregates, promotion of Aβ degradation/cl, and inhibition of Aβ aggregation and destabilization of aggregates. Several phenolic compounds are being evaluated in AD clinical trials, but none of them has been demonstrated to have unique therapeutic or preventative characteristics. More clinical trials and preventive interventions on these polyphenols to improve oral

bioavailability and brain penetration are needed to evaluate their effectiveness in AD.

Acknowledgement

The authors thank Al-Rafidain University College for supporting the project.

Conflicting interests

The authors declared no conflicts of interest.

Data sharing statement

N/A

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