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A REVIEW: THE PROTECTIVE EFFECTS OF DIETARY POLYPHENOLS ON ALZHEIMER'S DISEASE

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ABSTRACT

Alzheimer's disease (AD) is a progressive irreversible neurodegenerative disease in the hippocampus and cortex regions of the brain and is the most common cause of dementia in the elderly population among 40 million cases worldwide today, it is thought that this number will exceed up to 100 million by 2050. The disease is characterized by symptoms of memory loss, difficulty in speaking, decision making, learning, problem solving, and impaired perception of time and orientation. In its pathogenesis, the amyloid beta (Aβ) senile plaques accumulation in the extracellular synaptic spaces of the neurocortex, the formation of intracellular hyperphosphorylated tau protein deposition and neurofibrillary tangles (NFY) are important and triggered neurodegeneration mainly affects cognitive behavior and memory. Phenolic compounds are organic compounds containing a benzene ring to which one or more hydroxyl groups are attached. Studies have shown that regular consumption of polyphenols reduces the risk of developing neurodegenerative diseases. Studies have reported that polyphenols inhibit Aβ production and accumulation processes by interacting with different forms of amyloid structure. In this study, polyphenols and their therapeutic properties against AD will be discussed extensively.

Keywords: Alzheimer's Disease, Amyloid Beta, Neurodegeneration, Polyphenols

1. INTRODUCTION

Alzheimer's Disease (AD), characterized by Alois Alzheimer in 1907, is the main form of dementia and is a fatal neurodegenerative disease that develops and progresses under the influence of multiple factors including genetic, environmental and infectious mechanisms [1,2]. Dementia is the seventh most common reason of death today. The latest Alzheimer report shows 50 million people suffer from dementia and 1 trillion US dollars was spent on the treatment of dementia in the World [3]. It is predicted that this figure will increase and there will be 132 million dementia patients in 2050, and it is calculated that the expenditures for dementia treatment will double then [3]. AD affects more than 20 million people worldwide and this number will increase significantly in the future with the increase in the number of elderly people in the total population. Its prevalence is 10% around the age of 65 and 50% around the age of 85 [1]. AD affects large areas of the cerebral cortex and hippocampus. The abnormalities are usually first detected in brain tissue including the frontal and temporal lobes and then slowly progress to other areas of the neocortex at rates that are highly variable between individuals. AD is a chronic neurodegenerative disease that is the most common cause of dementia (60-80%). The most common causes of dementia in patients over the age of 65 are AD, vascular dementia and coexistence of vascular dementia and AD [3].

Approximately 10% of clinical dementia incidences are due to reversible causes such as metabolic anomalies (eg, hypothyroidism), nutritional disorders (eg, vitamin B12 deficiency, folate deficiency) or depression. It is estimated that 4.6 million new cases of AD develop every year all over the world. In molecular level, Alzheimer's disease is characterized by a wide variety of events such as errors in protein sequence and aggregation, oxidative stress, mitochondrial abnormalities and neuroinflammatory pathway [4]. Extracellular amyloid beta (Aβ) accumulation and intercellular hyperphosphorylated tau protein are accepted as the main pathological findings of AD [5]. Fibril tangles that are another neuropathological sign

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of AD, consist of abnormally hyperphosphorylated tau proteins [6]. In addition, the intracellular formation of extracellular accumulations and neurofibrillary tangles of Aβ plays an important role in oxidative stress, excitotoxicity, neuroinflammation and neurotransmitter deficiencies [7,8].
As a consequence of many mechanisms exist in the pathogenesis of AD, there is no approach that can prevent, completely treat or slow the progression of the disease, but drugs that delay the progression of the symptoms of the disease continue to be developed [9]. The developed treatment strategies are based on the approaches that constitute the pathogenesis of AD, especially acetylcholinesterase (AChE) and secretase inhibitors and tau therapies [10]. Acetylcholinesterase inhibitors (AChEIs) such as donepezil, galantamine and rivastigmine, and N-methyl D aspartate (NMDA) receptor antagonists such as memantine are approved by the US Food and Drug Administration (FDA) to improve the symptoms of Alzheimer's disease [11]. Donepezil, galantamine and rivastigmine are recommended for mild to moderate AD patients; and memantine is recommended for moderate to severe AD patients [12].
In addition to existing treatments, some herbal medicines, extracts and some active compounds can provide a therapeutic benefit against AD, thanks to their neuroprotective effect with cholinesterase inhibition activity, anti-tau, antioxidant, antiapoptosis, anti-inflammatory properties, and their ability to act as β-secretase inhibitors by affecting Aβ production [11,13]. It is considered that polyphenols found in plants can regulate Aβ production and aggregation by inhibiting amyloid self-assembly by stimulating α-secretase pathway or inhibiting β- and γ-secretase pathways [14]. Also, mitochondrial dysfunction, inflammation, hyperphosphorylated tau and Aβ accumulation in AD are associated with reactive oxygen species (ROS) [15]. ROS can occur through different mechanisms and has complex roles in accelerating AD development [16]. Further studies are needed to determine these complex roles of ROS in AD and to develop antioxidant-based therapeutic targets [16,17]. Here, the therapeutic properties of different polyphenols and their derivatives will be highlighted.

POLYPHENOLS

Polyphenols are secondary metabolites found in high amounts in fruits, vegetables, seeds and oils. Today, more than 10,000 natural polyphenols have been identified, and they are categorized into various groups according to the number of phenolic rings and the number of structural elements bonding these rings. These are mainly, phenolic acids and their derivatives, lignans, stilbenes, flavonoids which are also categorized into various subgroups [18,19].
The main common feature of all polyphenols is the presence of hydroxyl groups in the -ortho or -para positions required for redox reactions and that they contain more than one phenolic ring. These natural compounds have strong antioxidant properties that protect against oxidative damage due to their scavenging and metal chelating properties of free radicals produced by reactive oxygen species [18,20].
It was proven that polyphenols can have a neuroprotective effect in neurodegenerative diseases such as AD, prevent Aβ formation, and suppress the vicious circle between Aβ production and oxidative stress, with their anti-aging, cardiovascular protection and anti-inflammatory properties [20,21]. Previous findings show that all polyphenols have different effects on amyloid structure by interacting with different amyloid forms such as monomeric, oligomeric or fibril forms. It was stated that these compounds prevent the accumulation process by entering between the aromatic rings in the amyloidogenic protein structure [22,23]. Furthermore, it was discussed that polyphenols have the ability to stimulate the α-secretase pathway and inhibit the β- and γ-secretase pathway, and thus have the capacity to modulate Aβ production [24-26]. I was identified in AD studies that some polyphenols perform strong enzymatic inhibition in the Aβ production pathway, while some others prevent amyloid aggregation and fibril formation significantly [20-27]. E.g; quercetin and myricetin, which are some of the most known natural polyphenols exert significant effects by inhibiting the β-secretase enzymes. On the other hand, it was stated that epigallocatechin-3 gallate (EGCG), resveratrol, and curcumin, which are well-known polyphenols, form a

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non-covalent complex with the Aβ peptide and inhibit amyloid aggregation and also interact with the secretases or cyclooxygenase pathway [24]. It was emphasized that hydrophobic forces, aromatic stacking, electrostatic and aromatic interactions play an important role in the formation of Aβ, and the mechanism of polyphenolic compounds should be studied as predicting that they can be conjugated to Aβ formed in this way [28,29].

Phenolic Acids and AD

Phenolic or phenolcarboxylic acids are one of the main classes of plant phenolic compounds and are found in high concentrations in seeds, colored fruits such as berries and pomegranate, fruit skins, vegetables including onions and vegetable leaves as free or soluble conjugates. Phenolic acids are basically categorized into two subgroups as hydroxybenzoic and hydroxycinnamic acids [30,31]. Phenolic acids are phytochemicals commonly used in daily food intake, containing an aromatic ring bearing an acidic group and one or more hydroxyl groups. Phenolic acids are secondary metabolites that can often be found in plant-derived foods and form an important part of our daily diet [32-34]. These phenolic acids additionally form a group of secondary metabolites with redox and metal chelating properties that act as reducing agents [35]. Considering its potential health benefits such as antioxidant [36], antiviral [37], anticarcinogenic activities [38-40] and neuroprotective properties [41-51], it has attracted the attention of researchers due to these effects. It has therefore been demonstrated that phenolic acids can be used as health-promoting ingredients in functional foods and other products [52].
Chang et al. [41] have determined the protective effect of caffeic acid against AD that including caffeic acid in diet modulated Aβ accumulation, decreased the p-tau expression in the hippocampus and attenuated the APP expression as well as β-site APP cleaving enzyme in rat model of hyperinsulinemia. Mori et al. [42] and Yu et al. [43] have demonstrated that using gallic acid in the diet of transgenic mice with AD improved cognition, rescued learning and memory deficits and reduced Aβ aggregation. Also, Ogunlade et al. [44] have suggested that gallic acid was effective on ameliorating hippocampal neurodegeneration and cognitive stress in $AlCl_3$ induced rat model of AD. Shan et al. [45] have shown that implicating rosmarinic acid in diet of mice decreased tau phosphorylation and insoluble phosphorylated tau formation in the brain. Mori et al. [46] have determined that orally administrated tannic acid in transgenic mice with AD prevented cognitive impairment, decreased the cleavage of the β-carboxyl-terminal APP fragment and soluble APP-β production, as well as reduced β-site APP cleaving enzyme and diminished neuroinflammation. Hornedo-Ortega et al. [47] have found that protocatechuic acid inhibited Aβ aggregation and its preformed fibrils, also prevented the cell death triggered by Aβ toxicity in PC12 cell line model of AD. Guven et al. [48] have suggested that consumption of p-coumaric acid in rat model caused reduction of Aβ protein accumulation and decrease in neuroinflammation. Lee et al. [49] have demonstrated that sinapic acid application rescued neuronal cell death in hippocampus, attenuated memory impairment and oxidative stress as well as glial cell activation in Aβ-induced mice. Jha et al. [50] have shown that ellagic acid reduced neuroinflammation and oxidative stress, attenuated Aβ plaque and AChE levels and improved synaptic connectivity in rat model of sporadic AD. Ogut et al. [51] have determined that syringic acid decreased neuroinflammation and oxidative stress and improved neurobehavioral impairments in $AlCl_3$ induced rat model of AD.

Lignans and AD

Lignans are natural polyphenol compounds containing 2,3-dibenzyl butane skeleton that are attracting due to their strong antioxidant capacity and other biological and therapeutic properties on human health. Lignans are natural constituents known as the oxidative coupling product of β-hydroxyphenylpropane and are widely found as minor constituents in the plant kingdom [52]. Lignans are commonly available in

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edible plants, where they are synthesized via the phenylpropanoid pathway and following the biosynthesis of lignin [53]. Today, the amount and characterisation of lignans in various foods been evaluated [54]. It was reported that some lignans are known for their antitumor [55], antiviral [56], antibacterial [57] and immunosuppressive properties [58] as well as lignans have protective effect on cardiovascular diseases and diabetes [59]. Some studies [60-65] have proven the anti-neurodegenerative properties of lignans and neolignans.

Kantham et al. [60] have demonstrated the neuroprotective activity of biphenyl neolignane honokiol against AD in transgenic *Caenorhabditis elegans* by inhibiting Aβ aggregation and AChE, also scavenging DPPH radicals and chelating iron (II). Qi et al. [61] have determined that the use of arctigenin inhibited the hyperphosphorylated tau protein expression in hippocampus and provided protection against learning and memory deficits in Aβ-induced mice model of AD. Somani et al. [62] have shown that cubebin application prevented learning and memory deficits, also attenuated the AChE activity and oxidative stress level in scopolamine-induced mice model. Gu et al. [63] have determined that justicidin inhibited hyperphosphorylation of tau in AD; and enhanced activity of AMP-activated protein kinase, which is the key molecule for hyperphosphorylation of tau and elevated cell viability in Aβ-induced SH-SY5Y cell line. Huang et al. [64] have demonstrated that lignans, especially isolariciresinol and lyoniside showed a strong Aβ inhibition activity. Yang et al. [65] have suggested that two new dibenzocyclooctadiene lignans (L6-14, NL5-10) isolated from *Schisandra chinensis* exhibited protective effect against neurotoxicity in Aβ-induced PC12 cell line, and also increased the cell viability.

Stilbenes and AD

Stilbenes constitutes an important group of polyphenols that are quite common in plants. The most known compound is resveratrol (3,5,4'-trihydroxystilbene) which is found in large amounts in red wine and also in the grape skin [66]. Stilbenes are produced by plants in response to infections due to pathogens or various stress conditions. It has been detected in more 400 natural stilbenes in over 70 plant species, especially in grape, strawberry and peanut [67,68]. Some stilbenes have a great antioxidant activity and radical scavenging activity, and it was also reported that they prevent lipid peroxidation [69]. Also, stilbenes are associated with a wide range of pharmacological properties including antimicrobial and antifungal activity [70,71] and protective activity neurodegenerative pathologies such as AD [72-77].

Porquet et al. [72] have demonstrated that administration of *trans*-resveratrol in diet showed neuroprotective activity by reducing Aβ aggregation and tau hyperphosphorylation, attenuating cognitive impairment and increasing the lifetime in SAMP8 mice. Also, Karuppagounder et al. [73] have determined that oral supplementation of *trans*-resveratrol decreased Aβ plaque accumulation in Tg199589 transgenic mice model of AD. Caillaud et al. [74] have proven that use trans ε-viniferin decreased the Aβ aggregation and prevented neuroinflammation in the brain of transgenic APPswe/PS1dE9 mice. Hu et al. [75] have shown that miyabenol C reduced sAPPβ and soluble Aβ levels in the cortex and hippocampus of transgenic APP/PS1 mice. Chang et al. [76] and Hou et al. [77] have demonstrated that daily supplementation of pterostilbene in diet improved cognitive status and decreased neuroinflammation, cellular stress and AD markers in SAMP8 mice and C57BL/6 mice, relatively.

Flavonoids and AD

Flavonoids are one of the largest classes of phenolic compounds having a group of benzo-γ-pyrone derivatives [78]. They are synthesized by all vascular plants and are found in the composition of fruits, vegetables, seeds, herbs, whole grains and tea [79]. It is estimated that over 6500 flavonoids were identified in this group [80]. Flavonoids are divided into 6 subgroups: flavonols, flavones, flavanones, flavan-3-ols (catechins), isoflavones and anthocyanidins [81]. It was emphasized that flavonoids have

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many biological benefits including antioxidant [82], anti-inflammatory [83], antiatherogenic [84,85] and anticarcinogenic activities [86,87]. More recently, dietary intake of flavonoids has been associated to early proof that the onset of some neurodegenerative disorders such as dementia and AD may be postponed [88-96].

Jimenez-Aliaga et al. [88] have demonstrated that quercetin and rutin inhibited the Aβ formation and disaggregated Aβ fibrils, reduced the β-secretase enzyme activity and ROS generation in H_2O_2-treated APPswe cells. Ho et al. [89] have shown that dietary quercetin-3-O-glucuronide extracted from Cabernet Sauvignon red wine reduced the generation of Aβ peptides in transgenic Tg2576 mice. DeToma et al. [90] have proven that myricetin was effective against metal associated Aβ generation and modulated Aβ aggregation as well as neurotoxicity in human neuroblastoma cells and in vitro. Sharoar et al. [91] have determined that kaempferol-3-O-rhamnoside inhibited fibrilogenesis of Aβ in SH-SY5Y cell line, but as a consequence of this inhibition caused an oligomeric species accumulation, yet these aggregates were smaller, soluble, non-β-sheet formed and non-toxic. Ahmad et al. [92] have demonstrated that the use of fisetin decreased the accumulation of Aβ peptides, β-secretase enzyme expression and hyperphosphorylation of tau protein, and prevented the neuroinflammation, also improved the cognitive activity by increasing the presynaptic and postsynaptic proteins in C57BL/6N mice. Tarozzi et al. [93] have shown that cyanidin 3-O-glucoside inhibited the spontaneous aggregation of Aβ into oligomers, also prevented the neuronal loss and synaptic dysfunction in SH-SY5Y cell line. Wang et al. [94] have proven that dietary supplementation of naringin improved cognitive and locomotor activities, reduced scattered senile plaques and moderated disturbances in brain energy metabolism of APPswe/PSdE9 transgenic mice. Balez et al. [95] have suggested that apigenin showed anti-inflammatory effect as protecting neurites and preventing cellular death by promoting nitric oxide and cytokine release in inflammatory cells in human induced pluripotent stem cells. Bieschke et al. [96] have determined that epigallocatechin gallate (EGCG) inhibited the fibrilogenesis of Aβ and α-synuclein, which is associated with cognitive impairment, and converted these fibrils into smaller aggregates in HEK-293 cell line. Table 1 indicates the summarized results of studies of each polyphenol groups that were highlighted in this review.

Table1. The effect of polyphenols on AD

Polyphenols	***Sample***	***Intervention***	***Summary of Findings***	***Ref.***
Apigenin	Stem cell model of AD	Inoculated into stem cells (10 μM)	• Performed anti-inflammatory effect via protecting neurites • Prevented neuronal loss	95
Arctigenin	Mouse model of AD (ICR)	Orally administrated (150 mg/kg b.w./day)	• Attenuated behavioral impairments • Inhibited tau phosphorylation in the hippocampus	61
Caffeic acid	Rat model of hyperinsulinemia	Orally administrated (30 mg/kg b.w./day)	• Ameliorated memory and learning impairments • Decreased the p-tau expression in the hippocampus • Attenuated APP expression and β-site APP cleaving enzyme	41
Cubebin	Mouse model of AD	Orally administrated (50 mg/kg b.w./day)	• Prevented scopolamine-induced cognitive impairment • Inhibited AChE activity and decreased oxidative stress	62
Cyanidin 3-O-glucoside	SH-SY5Y cell line	Inoculated into the cell line (25, 50 and 100 μM)	• Inhibited spontaneous Aβ aggregation • Prevented neuronal loss and synaptic dysfunction	93
Ellagic acid	Rat model of sporadic AD	Orally administrated (50 mg/kg b.w./day)	• Diminished oxidative stress, neuroinflammation, AchE and Aβ level • Normalized abnormal behavioral	50

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			representations	
(-)-epi-gallo-catechine gallate	HEK-293 cell line	Inoculated into the cell line (50 μM)	• Inhibited Aβ and α-synuclein fibrilogenesis • Converted large Aβ and α-synuclein fibrils into smaller	96
Fisetin	Mouse model of AD (C57BL/6N)	Intraperitoneal injection (20 mg/kg b.w./day)	• Decreased Aβ accumulation, BACE-1 expression and tau phosphorylation • Prevented neuroinflammation • Improved memory	92
Gallic acid	Transgenic mouse model of AD (APP/PS1)	Orally administrated (20 mg/kg b.w./day)	• Reversed learning and memory impairment • Decreased Aβ deposits, reduced β-secretase activity, inhibited neuroinflammation	42
Gallic acid	Transgenic mouse model of AD (APP/PS1)	Orally administrated (30 mg/kg b.w./day)	• Improved memory and learning • Reduced Aβ aggregation	43

Table1. (Continued)

Polyphenols	***Sample***	***Intervention***	***Summary of Findings***	***Ref.***
Gallic acid	Rat model of AD ($AlCl_3$ induced)	Orally administrated (100 mg/kg b.w./day)	• Ameliorated memory impairment and learning deficit • Restored stress markers	44
Honokiol	Transgenic *Caenorhabditis elegans* model of AD	Inoculated (10, 100 and 1000 μM)	• Inhibited AChE and Aβ aggregation • Performed DPPH scavenging and chelating iron (II) activity	60
Justicidin	SH-SY5Y cell line	Inoculated into the cell line (62.5, 125, 250, and 500 nM)	• Inhibited tau phosphorylation • Induced autophagy by regulating GSK-3β and AMP-activated protein kinase	63
Kaempferol-3-O-rhamnoside	SH-SY5Y cell line	Inoculated into the cell line (10, 20, 30, 40 and 50 μM)	• Reduced Aβ mediated cytotoxicity • Inhibited fibrilogenesis and accumulation	91
Miyabenol C	Transgenic mouse model of AD (APP/PS1)	Intracerebroventricular injection (0.6μg/g)	• Reduced Aβ and sAPPβ levels in the brain • Inhibited of β-secretase activity	75
Myricetin	SK-N-BE(2)-M17 cell line	Inoculated into the cell line (20 μM)	• Diminished metal induced Aβ generation • Modulated Aβ aggregation	90
Naringin	Transgenic mouse model of AD ($APP^{swe}/PS^{\Delta E9}$)	Orally administrated (100 mg/kg b.w./day)	• Attenuated plaque burden • Improved cognitive functioning	94
p-coumaric acid	Sprague-Dawley rats	Orally administrated (100 mg/kg b.w./day)	• Reduced Aβ aggregation • Decreased neuroinflammation	48
Pterostilbene	Mouse model of AD (SAMP8)	Orally administrated (120 mg/kg b.w./day)	• Reduced cellular stress, inflammation and AD pathology	76
Pterostilbene	Mouse model of AD (C57BL/6)	Orally administrated (400 mg/kg b.w./day)	• Attenuated cognitive impairment • Inhibited microglia activation	77
Protocatechuic acid	PC12 cell line	Inoculated into the cell line (2, 5, 10, 20, 50 and 100 μM)	• Inhibited Aβ and α-synuclein aggregation and fibrillation • Prevented cell death triggered by their toxicity	47
Quercetin *Rutin*	APPswe cell line	Inoculated into the cell line (25, 50 and 100 nM each)	• Both inhibited Aβ formation and disaggregated Aβ fibrils • Both decreased ROS generation • Rutin inhibited β-secretase enzyme activity	88
Rosmarinic acid	Mouse model of AD (C57BL/6)	Orally administrated (2 mg/kg b.w./day)	• Decreased tau phosphorylation and insoluble phosphorylated tau in the brain	45
Sinapic acid	Mouse model of AD (ICR)	Orally administrated (10 mg/kg b.w./day)	• Rescued neuronal cell death • Attenuated memory impairment	49
Syringic acid	Rat model of AD ($AlCl_3$ induced)	Orally administrated (25 mg/kg b.w./day)	• Reduced neuroinflammation and oxidative stress • Diminished neurobehavioral impairments	51
Tannic acid	Transgenic mouse model of AD (APP/PS1)	Orally administrated (30 mg/kg b.w./day)	• Prevented behavioral impairment • Mitigated Aβ deposition	46
Trans ε-viniferin	Transgenic mouse model of AD (APP/PS1)	Orally administrated (10 mg/kg b.w./day)	• Reduced size and density of Aβ deposits • Decreased reactivity of astrocytes and	74

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			microglia	
Trans-Resveratrol	Mouse model of AD (SAMP8)	Orally administrated (1 g/kg b.w./day)	• Reduced cognitive impairment • Diminished Aβ burden and tau phosphorylation	72
Trans-Resveratrol	Transgenic mouse model of AD (Tg19959)	Orally administrated (300 mg/kg b.w./day)	• Diminished Aβ plaque formation	73

2. CONCLUSIONS

In conclusion, some dietary polyphenols described and discussed in this review have demonstrated many important therapeutic properties against AD. From the worldwide public health viewpoint, the daily consumption of plant-based aliments and their derivates including berries, citrus fruits, pomegranate, grape, herbs, nuts, coffee, tea, and wine have become the main tool for prevention of AD. This has encouraged studies through the comprehending of the mechanisms at the principle of such precautions. The aforesaid initiatives have led to the recognition of such mechanisms including antioxidant capacities, reducing ROS content, capability to prevent the fibrilogenesis of Aβ and its accumulation, inhibition the AChE activity. Taking everything into account, these findings confirm the potential of dietary polyphenols as active agents against AD as well as other neurodegenerative disorders and should inspire scientists to use the data for the design of potential therapies for the mentioned disorders.

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