

# The Role of Natural Compounds in the Treatment of Alzheimer's Disease

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## Review Article

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## Abstract

Diseases related to aging burden irreparable damage to elderly. Interestingly, aging has an increasing trend in world population. Therefore, there is a dire need to solve problem. Alzheimer disease is one of the most common neurodegenerative diseases in worldwide. Based on previous studies, there is no promising treatment for Alzheimer disease and this treatment cannot inhibit disease progress. Given that induction of oxidative stress and inflammation during Alzheimer disease, thus their abrogation is an ideal strategy to treat Alzheimer disease. It have been reported that natural products have therapeutic effects against Alzheimer disease and in other word they are promising therapeutic options for patients with Alzheimer disease. In addition, they can use in all patients due to simple access and low cost. In this review study, we describe effects of natural products in treatment of Alzheimer disease.

**Keywords:** Aging; Alzheimer disease; Neurodegenerative diseases; Natural products

## Introduction

Alzheimer disease is a neurodegenerative disorder that is considered as a dementia along with dysfunction in memory particularly working and episodic memory [1,2]. Generally, Alzheimer disease is observed as sporadic (commonly) and familial (rarely and due to mutations in genes of amyloid  $\beta$  precursor protein, presenilin 1 and presenilin 2 [3]. Synapses losing, increase of extracellular amyloid beta, increase of intracellular neurofibrillary tangles caused by aggregation of hyperphosphorylated Tau, formation of senile plaques commonly occur during Alzheimer disease [4]. In addition, it has been reported

that AD patients, who had mild cognitive impairment (MCI) there is high level of isoprostanes as products of polyunsaturated fatty acid oxidation [5]. It has been estimated that 5.3 million Americans suffered from AD so that 84,767 of patient are died, in other word AD is a main reason of mortality among elderly [6]. In 2013, it has been reported that there is 160287 Portuguese people, who suffered from Alzheimer's disease. This numbers contain 5.91% from individuals aged  $\geq 60$  years [7]. According to a study in Taiwan, there was 5.63/1,000 persons AD patient in 2005 so that its incidence reached to 8.17/1,000 persons in 2010. This incidence led to spend Taiwan dollars (NT\$) 205,413-227,110 in order to hospitalization

of patients [8]. Study on costs related to health care in AD patients was revealed that \$226 billion pay to treat these patients [6]. Based on these finding, AD is a serious threat for health human at near future. Brain is susceptible to oxidative stress due to lack of a potential antioxidant defense besides it is main source of ROS thus under any oxidative conditions, brain damage is very possible [2]. Based on previous studies, synaptic dysfunction and neuronal death result from increase of free radical in cytoplasm [9-12]. In a study, it has been showed that AD patients, who had mild cognitive dysfunction, have low level of SOD and GPX and high level of MDA in serum. Indeed, oxidative stress is a significant mark in these patients [13]. Location of amyloid precursor protein and amyloid  $\beta$  in mitochondria can be affective in their dysfunction particularly in neurons of hippocampus [14-16]. In other word, mitochondria dysfunction is one of the main reasons AD pathology so that ATP synthesis inhibition, induction of mitochondrial permeability transition pore and apoptosis induction through cytochrome c releasing and apoptosis-inducing factor into cytoplasm and activation of caspase cascade occur during AD. It seems that entering of  $Ca^{2+}$  to mitochondria has pivotal role in initiation of these events [17]. Generally, mtDNA is susceptible to damages related to ROS due to lack of protective proteins such as histone, efficient DNA repair system and ROS generation in their vicinity that lead to increase of oxidative damage in mtDNA of neurons related to an AD patients [18]. Based on previous studies, it have been confirmed role of stress oxidative in damage to mtDNA [16,19]. In addition, it have been observed high level of mutations such as 5-kb deletion in mtDNA obtained from brain of AD patients [16,20]. According to recent data about association between neuroinflammation and AD, it has been revealed that immune system-mediated actions was observed during AD so that it can be one of the therapeutic goals to treat AD [21]. Indeed, misfolding and aggregation of amyloid protein leads to a potential immunogenicity that induces inflammation in brain of AD patients about 10-15 years before any clinical manifestation [22]. Induced inflammation is main factor to act microglia that it is very affect in neuronal and synaptic damage, but reaction of microglia can be a defense act to clear toxic amyloid- $\beta$  species [23,24]. Protein

carbonylation occur at high level in proteins such as glutamine synthase, creatine kinase and ubiquitin carboxy-terminal hydrolase L-1 in brain's different regions include hippocampus, inferior parietal lobe, cerebellum and frontal and temporal lobes [25-27]. Neurodegenerative processes commonly occur in postsynaptic regions caused by calcium influx and oxidative stress induction through activation of glutamate receptors [21]. In addition, reduced metabolic activity leads to oxidative damage and ultimately deleterious of mitochondrial components during AD [16,28]. Indeed, given that reduced energy metabolism is considered as an abnormality during AD therefore low glucose metabolism at baseline and longitudinal glucose metabolism decline can be useful tool to monitor diagnosis and predicting of MCI [29-31]. Despite performed efforts, there are many challenges to treat Alzheimer disease; in fact current therapeutic strategies to attenuate AD cannot inhibit progress of disease [32]. Concomitant by increase of AD patients but promising therapy had not dramatically development, although acetylcholinesterase (AChE) inhibitors still use among these patients but they have not prominent effect to inhibit AD progress [33]. Natural products are one of potential source in order to achieve a useful therapy due to be available, low cost and to have antioxidant and anti-inflammatory properties [33]. In other word, in order to diminishing of costs related to Alzheimer treatment use of natural produce with neuroprotective property is need, however it has dire need to investigate either in vitro or in vivo studies [34,35]. Use of an antioxidant regimen can be a useful method to abrogate ROS and their complication in AD so that their administration led to reduction of AD progression [28]. In this study, we reviewed the role of natural compounds in treatment of Alzheimer.

### Review Method

In order to obtain better results, we searched papers related to Alzheimer using keywords such as natural product and Alzheimer disease, natural compounds and Alzheimer disease, animal model of AD and natural product in databases of web of science, PubMed and Scopus from 2000 to now. In final, the papers were read and summarized (Table 1).

Compound	AD model	Finding(s)	References
Quercetin	Drosophila model with A $\beta$ accumulation	Up-regulation of genes related to cell cycle and DNA replication	[36]
	3xTg-AD mice	Enhancement of histological changes and cognitive and emotional dysfunction	[37]
	APPswe/PS1dE9 Tg mice	Reduction in senile plaque, improvement of mitochondrial dysfunction by AMPK activation and enhancement of cognitive deficit	[38]

	Aged wild-type mice, AD patients in early-stage	Improvement of memory recall	[39]
Epicatechin	AD mice with tau abnormality	To have protective effect in reduction of tau abnormal from	[40]
Ellagic acid	Rats with AD caused by beta amyloid25-35 microinjection	Promotion of acetyl cholinesterase reactivation	[41]
Caffeic acid	A $\beta$ <sub>25-35</sub> -induced AD mouse	Inhibition of cognitive deficit, reduction of lipid peroxidation and nitric oxide level	[42]
	AD rats	To have antioxidant and anti-inflammatory effects, cognitive dysfunction improvement, regulation expression and phosphorylation of p53	[43]
Curcumin	AD rats	Binding to iron and copper, reduction of A $\beta$ toxicity and inflammation	[44]
	Alzheimer transgenic APPSw mouse model	To have antioxidant and anti-inflammatory effect, reduction of A $\beta$ , GFAP and microgliosis	[45]
	APPswe/PS1dE9 AD mice model	Senile plaques reduction, inhibition of dystrophic dendrites	[46]
Soy isoflavones	ovariectomized-induced Alzheimer's disease	Spatial learning and memory improvement	[47]
	d-galactose-induced aging in C57BL/6J mice	Reduction of stress oxidative and A $\beta$ toxicity	[48]
Genistein	A $\beta$ <sub>(1-40)</sub> -induced AD model in rats	To have anti-oxidant effects, improvement of cognitive dysfunction	[49]
Naringenin	AD-TNDCI rat model	Reduction of stress oxidative and cognitive dysfunction	[50]
Epigallocatechin-3-gallate	Alzheimer transgenic mice	Reduction of A $\beta$ generation	[51]
	A $\beta$ -induced AD rats	Improvement of psychomotor coordination index and spatial Y-maze alternation	[52]
	APPsw Tg AD mice	Reduction of A $\beta$ deposition and plaques, improvement of tau pathology and behavioral deficit	[53]
	human SH-SY5Y neuroblastoma cell line	Iron chelating activity, increase of mRNA and protein levels of transferrin receptor, reduction of immature and full-length cellular holo-APP forms	[54]
Hesperidin	Three-month-old APPswe/PS1dE9 transgenic mice	To have antioxidant effect, increase of mitochondrial complex I-IV enzymes activities and GSK-3 $\beta$ phosphorylation, enhancement of locomotor activity, reduction of cognitive dysfunction	[55]
Gallic acid	A $\beta$ -induced AD rats	Improvement of hippocampal long-term potentiation and histological damages	[56]

AMPK: 5' AMP-activated protein kinase; AD-TNDCI: Alzheimer's disease-type neurodegeneration with cognitive impairment; APP: Amyloid precursor protein; GSK-3 $\beta$ : Glycogen synthase kinase-3 $\beta$

Table 1: Effects of natural product in treatment of AD.

### Mechanism of Neuronal Cell Death in AD

Oxidative stress is the imbalance between pro oxidants and antioxidant factors that lead to accumulation of reactive oxygen species (ROS) [36]. This reactive species

can lead to cell membrane lipid destruction, DNA cleavage, oxidation of proteins, and finally apoptosis [57]. Apoptosis is the predominant type of neuronal cell loss observed in AD [58]. Apoptotic cell death signaling can be divided into two major pathways; intrinsic (or mitochondrial) pathway

and extrinsic (or death receptor-mediated) pathways [59]. Apoptosis in mammalian cells regulates by a large number of proteins (Figure 1). In the intrinsic pathway, stimuli acts directly or indirectly on mitochondria and affects mainly Bcl-2 family and caspase [60]. Bcl2 superfamily consists of both pro-apoptotic (such as Bax, Bad, and Bak) and anti-apoptotic (such as Bcl-2 and Bcl-xL) proteins. Decrease of anti-apoptotic protein and/or increase of pro-apoptotic factors results in disruption of mitochondria membrane potential, swelling of mitochondrial membrane, and release of cytochrome c to cytoplasm [61]. In cytoplasm, cytochrome c forms a multi-molecular holoenzyme complex with apoptotic protease activating factor 1 (Apaf1), which cleaves procaspase-9 to its active form. Active caspase-9 then cleaves procaspase-3 and initiates the caspase cascades [62]. Extrinsic pathway of apoptosis involves the interaction of death signals, for example tumor necrosis factor (TNF- $\alpha$ ) with death receptors, such as tumor necrosis factor receptors 1 (TNFR1), and formation of death-inducible signaling complex that activates caspase-8, which could also cleave procaspase-3 to its active form [63]. Activated caspase-3, in both intrinsic and extrinsic pathways, activates poly (ADP-ribose) polymerase (PARP) and other death substrates, such as APP, PS1 and PS2 proteins [64]. Stress conditions also affect the folding of proteins in endoplasmic reticulum (ER) lumen [65]. Three main ER pathways involved in folding include inositol-requiring enzyme 1 (IRE1), protein kinase RNA-like ER kinase (PERK), and activating transcription factor 6 (ATF6) [66]. ER stress response is mediated via three different signaling pathways: unfolded protein response (UPR), which increases the level of chaperones; ER-associated protein degradation (ERAD) that degrades the misfolded proteins by activating ubiquitin/proteosomal pathway; and ER overload response (EOR) which is induced when ER is overload with proteins that are not transported to Golgi complex [67]. Under ER stress conditions, glucose-regulated protein 78 (GRP78) which is an ER chaperone, dissociates from ATF6, PERK, and IRE1 and binds to malformed proteins to facilitate their folding [68]. C/EBP homologous protein (CHOP) together with caspase-12, which are ER resident caspases, and calpain mediate ER stress-induced apoptosis by affecting executioner caspases, such as caspase-3 [69,70]. While accumulation of unfolded proteins in ER provokes these pathways, accumulation of misfolded proteins in the cytosol leads to increased expression of heat shock proteins (HSPs) which act as molecular chaperons [71]. HSPs expression is induced by several stimuli including heat shock, ischemia damage, infection, and heavy metals [72]. HSPs may protect cells by mechanisms unrelated to their chaperone function through inhibition of apoptosis [73]. Stress-inducible Hsp70 is a prominent cytoprotective factor that protects

the sensitive sites of the target proteins and thereby acts as a cytoplasmic "antioxidant" [74]. In addition to mitochondria- and ER-resident proteins, many stress-sensing transcription factors are also activated in AD. NF-E2 related factor 2 (Nrf2) is a central transcription factor involved in transcriptional activation of phase II detoxifying enzymes via antioxidant response element (ARE) [75]. Release of Nrf2 from its cytoplasmic inhibitor, Kelch-like ECH-associated protein 1 (Keap1), leads to activation of Nrf2 and its translocation to nucleus, where it activates transcription of ARE-driven genes, such as Hsp32 and  $\gamma$ -glutamylcysteine synthetase ( $\gamma$ -GCS) [76]. Nuclear factor- $\kappa$ B (NF- $\kappa$ B) is another transcription factor that is activated by TNF- $\alpha$ , interleukin 1 $\beta$  (IL-1 $\beta$ ) and lipopolysaccharide (LPS) (canonical pathway) or by LT $\alpha$ / $\beta$ , CD40 ligand (non-canonical pathway) [77]. In unstimulated cells, NF- $\kappa$ B is sequestered inactive in cytoplasm by binding to I $\kappa$ Bs (Inhibitor of  $\kappa$ B). Activation of the NF- $\kappa$ B involves the phosphorylation of two serine residues located on I $\kappa$ B regulatory domain by I $\kappa$ B kinase (IKK) and release of NF- $\kappa$ B [78]. In nucleus, NF- $\kappa$ B induces production of different mediators, like nitric oxide (NO), and regulates a number of inflammation- and oxidative stress-related genes, such as cyclooxygenase 2 (COX-2), superoxide dismutase (SOD), glutamate receptors, growth factors (brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF)), and cytokines (TNF- $\alpha$  and TNFR) [79,80]. NF- $\kappa$ B signaling is inhibited by peroxisome proliferator-activated receptor  $\gamma$  (PPAR $\gamma$ ), a transcription factor of the nuclear hormone receptor superfamily [81]. PPAR $\gamma$  agonists attenuate effectively oxidative stress, inflammation and apoptosis in the central nervous system [82]. Mitogen-activated protein kinase (MAPK) cascades are other major signaling pathways involved in cell proliferation, differentiation and adaptation [83]. The p38 MAPK signaling has been widely accepted as a cascade contributing to neuroinflammation, excitotoxicity, synaptic plasticity and tau phosphorylation [84]. Inhibitors of ERK and p38 MAPK improve spatial learning and memory impairment in A $\beta$ - injected rats by increasing phosphorylated cAMP-response element binding protein (CREB) level [85]. JNK protein is a stress activated protein kinase with several targets including Bcl family members and microtubule associated proteins, such as tau [86]. Another important signaling pathway involved in AD is Wnt pathway. Wnt signaling plays an important role in normal neural development and maintenance of neuronal homeostasis, synaptic plasticity, axonogenesis and establishment of brain polarity [87]. Activation of the Wnt pathway attenuates cytosolic glycogen synthase kinase 3 $\beta$  (GSK-3 $\beta$ ) activity via protein kinase C (PKC) enzyme, thereby prevents phosphorylation and degradation of  $\beta$ -catenin and increases its nuclear translocation [88]. In nucleus,  $\beta$ -catenin interacts with TCF/LEF family

transcription factors to promote specific gene expression [89]. These gene products are important in determining cell's fate during normal development and in maintaining homeostasis [90]. Several studies have shown that PS-1 protein could form high molecular weight complexes with GSK-3 $\beta$  and  $\beta$ -catenin protein [91]. It has been suggested that PS-1 inherited mutations may affect the levels, trafficking or the phosphorylation state of cytosolic  $\beta$ -catenin [92] (Figure 2).

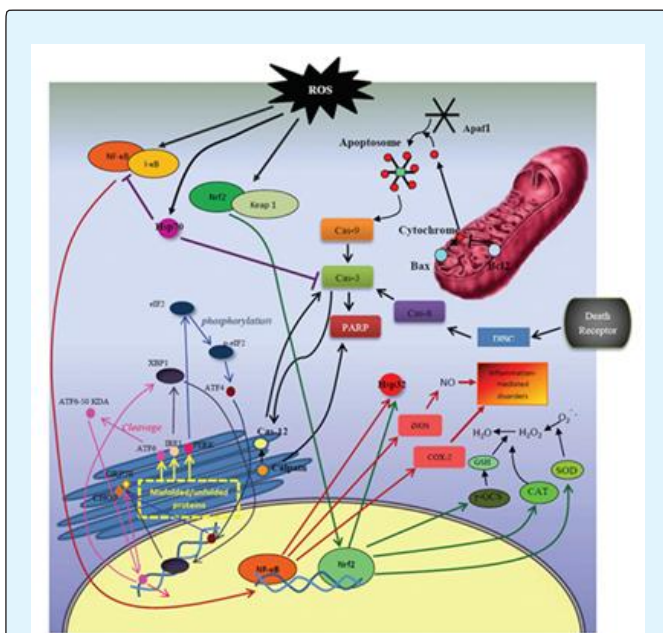


Figure 1: Mechanism of apoptotic pathways and ER stress.

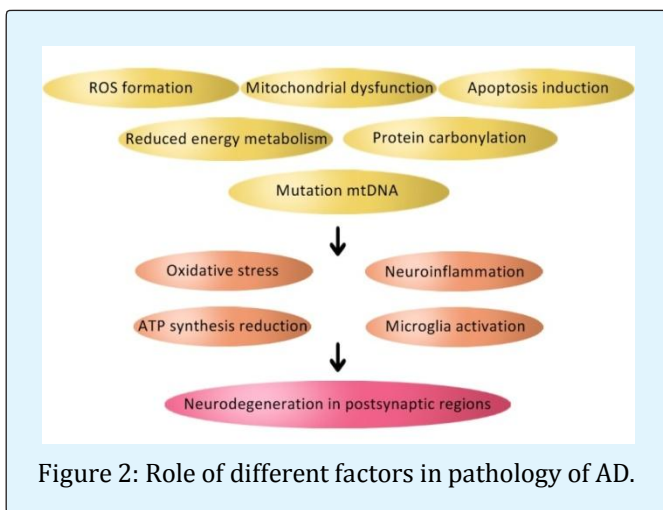


Figure 2: Role of different factors in pathology of AD.

## Role of Natural Product to Treat AD

In a study, it has been reported that treatment of drosophila with AD pathogenesis such as reduced lifespan, impaired locomotive ability, lack of memory and learning with quercetin could diminish problems induced by A $\beta$  accumulation by expression of genes related to cell cycle and DNA replication, which inhibited their expression by A $\beta$  accumulation [93]. In order to evaluation of quercetin neuroprotective effect against Alzheimer's disease, it was injected to 3xTg-AD mice. The results showed that it leads to reduction of extracellular  $\beta$ -amyloidosis and tauopathy in hippocampus and amygdale. In addition, reduction of astrogliosis and microgliosis were observed. It has also a obvious effect in reduction of paired helical filament (PHF),  $\beta$ -amyloid ( $\beta$ A) 1-40 and  $\beta$ A 1-42 levels and BACE1-mediated cleavage of APP (into CTF $\beta$ ). These effects resulted in improvement of learning ability and spatial memory [37]. Experiment about abrogation of Amyloid- $\beta$  (A $\beta$ )-induced mitochondrial dysfunction by quercetin was revealed that it has potential effect in reduction of learning and memory deficits as well as senile plaques. Mitochondrial dysfunction improved through restoration of mitochondrial membrane potential and ATP level, reduction of reactive oxygen species. Treatment with quercetin led to increase of AMP-activated protein kinase (AMPK) activity [38]. Study on quercetin effect (as long-term intake) on memory recall in aged wild-type mice was showed that quercetin has prominent effect in recovery of memory. Interestingly, when AD patients, who were in early-stage of Alzheimer, were treated by Quergold, a new cultivar of hybrid onion as a quercetin-rich source, it led to improvement of memory recall [39]. According to study performed by George, et al. 2013 treatment with cinnamaldehyde and epicatechin lead to inhibition of tau aggregation by interaction with two cysteine residues in tau. In addition, cinnamaldehyde and its oxidized form, epicatechin, protect tau from oxidation through reduction of ROS and hydrogen peroxide. It had also inhibitory effect against formation of high molecular weight species affecting in stimulation of tangle formation [40]. Administration of ellagic acid to beta amyloid-induced-Alzheimer rats reduced symptoms of Alzheimer disease so that it could improve acetylcholinesterase reactivation in dorsal hippocampus [41]. Study on protective effect of caffeic acid against AD mouse model induced by A $\beta$ <sub>25-35</sub> was revealed that this compound had promising effect due to improvement of cognitive deficit as well as reduction of lipid peroxidation and nitric oxide formation in brain [42]. In another study, it has been confirmed that caffeic acid leads to recovery of learning problems and enhancement

of cognitive function. In addition, biochemical evaluations were revealed reduction of acetylcholinesterase activity and nitrite generation, expression of nuclear factor- $\kappa$ B-p65 protein and caspase-3 activity after administration of caffeic acid. Interestingly, it regulated p53 protein expression and its phosphorylated form rats with AD. Finally, these findings were showed that it can be a promising compound to treat Alzheimer disease [43]. Given that, curcumin has high affinity to bind iron and copper thus it can reduce stress oxidative in brain and ultimately inhibit A $\beta$  toxicity and inflammation induced by NF- $\kappa$ B [44]. Study on Alzheimer transgenic APP<sup>Sw</sup> mouse model was showed that treatment with curcumin has anti-Alzheimer effects in this animal model so that it had anti-oxidative and anti-inflammatory effects by reduction of oxidized proteins and elevated interleukin-1 $\beta$  levels in brain. In addition, its low dose led to reduction of GFAP (an astrocytic marker), insoluble and soluble A $\beta$  as well as plaques. Low dose of curcumin also inhibited microgliosis [45]. Experiment on APP<sup>swe</sup>/PS1dE9 mice treated by curcumin was revealed that curcumin reduces senile plaques in the brain that indicated potent disaggregation effect and in addition it had protective effect against dystrophic dendrites by improvement of abnormal curvature and dystrophy size [46]. Administration of soy isoflavones to rats with ovariectomized-induced Alzheimer's disease leads to obtain promising findings about effects of soy isoflavones against Alzheimer disease because it resulted in improvement of spatial learning and memory [47]. In addition, it has been reported that d-galactose (DG)-induced aging leads to induction of stress oxidative and apoptosis in brain by increase of thiobarbituric acid-reactive substances and soluble extracellular receptors for advanced glycation end products in serum and brain. Moreover, increase of Bax expression, caspase-3 protein activity, A $\beta$ , presenilin-1 and  $\beta$ -site amyloid precursor protein cleaving enzyme-1 in brain C57BL/6J mice were observed. While, treatment with soy isoflavones normalized these complications and enhanced problems associated with Alzheimer's disease [48]. Study on role of genistein in treatment of Alzheimer disease showed that it diminishes changes occurred during induction of Alzheimer by A $\beta$ <sub>(1-40)</sub>-injection in rats such as increase of MDA and nitrite levels, reduction of SOD activity that led to improvement of cognitive dysfunction [49]. In another study, it has been reported that naringenin results in inhibition of stress oxidative through reduction of 4-hydroxynonenal, malonaldehyde, thiobarbituric reactive substances, hydrogen peroxide, protein carbonyl, and increment of glutathione. In addition, it led to normalization of enzymes related to antioxidant defense such as glutathione peroxidase, glutathione reductase, glutathione-S-transferase, superoxide dismutase, catalase and Na<sup>+</sup>/K<sup>+</sup>-ATPase activity in the hippocampus of rats

with Alzheimer disease induced by intracerebroventricular-streptozotocin. In addition, determination of choline acetyltransferase positive neuron showed that this compound inhibits its loss. Interestingly, dysfunction in spatial learning and memory improved after treatment with naringenin [50]. Epigallocatechin-3-gallate is a natural compound that can be a promising agent to treat Alzheimer. Using two Alzheimer transgenic mice include murine neuron-like cells (N2a) transfected with the human "Swedish" mutant amyloid precursor protein (APP) and in primary neurons derived from Swedish mutant APP-over expressing, mice (Tg APP<sup>sw</sup> line 2576) were confirmed that epigallocatechin-3-gallate leads to reduction of A $\beta$  generation. This finding was obtained by increase of cleavage in  $\alpha$ -C-terminal fragment of APP as well as increment of N-terminal APP cleavage product and soluble APP- $\alpha$  due to increase of  $\alpha$ -secretase activity and hydrolysis of tumor necrosis factor  $\alpha$ -converting enzyme. In addition, epigallocatechin-3-gallate reduced A $\beta$  level and plaques related to promotion of nonamyloidogenic  $\alpha$ -secretase proteolytic pathway after its administration in Tg APP<sup>sw</sup> transgenic mice [51]. In a study, in order to modeling of cognitive dysfunction during Alzheimer disease,  $\beta$ -amyloid was injected into rat brain and then treatment with epigallocatechin-3-gallate showed that reduction of cognitive deficit occur through improvement of psychomotor coordination (PMC) index and spatial Y-maze alternation at the end of study [52]. In another experiment, it has been showed that oral administration of epigallocatechin-3-gallate to "Swedish" mutant amyloid precursor protein over expressing (APP<sup>sw</sup>, Tg) mice leads to reduction of A $\beta$  deposition (A $\beta$ <sub>1-40</sub> and <sub>1-42</sub> soluble and insoluble forms) and plaques in cingulate cortex, hippocampus, and entorhinal cortex. Evaluation of tau pathology was showed that it reduced sarkosyl-soluble phosphorylated tau isoforms. In addition, in behavioral study improvement of cognitive impairment was confirmed [53]. Analysis of role of epigallocatechin-3-gallate on regulation of iron metabolism-related proteins APP and transferrin receptor in human SH-SY5Y neuroblastoma cells was confirmed that it has prominent iron-chelating activity and increases mRNA and protein levels of transferrin receptor. Moreover, reduction in immature and full-length cellular holo-APP forms was observed [54]. Wang, et al. 2014 reported that treatment with hesperidin normalize mitochondria dysfunction and oxidative stress in three-month-old APP<sup>swe</sup>/PS1dE9 transgenic mice as an animal model of Alzheimer disease. In this study was showed that hesperidin has potential effect in increase of anti-oxidative defense and mitochondrial complex I-IV enzymes activities as well as glycogen synthase kinase-3 $\beta$  (GSK-3 $\beta$ ) phosphorylation. In addition, an obvious improvement in learning and memory deficits and locomotor activity was showed. However,

hesperidin was unable to reduce A $\beta$  deposition [55]. According to study on effect of gallic acid in treatment of Alzheimer disease, it has been showed that this compound leads to improvement of hippocampal long-term potentiation and histological changes subsequently its administration to rats with Alzheimer disease induced by A $\beta$  injection [56].

## Conclusions

As shown in figure 1 and 2, increase of ROS level triggers neurodegeneration spatially in postsynaptic regions so that there are the collections of events to do this possess. Given that above studies, we found that treatment with compounds obtained from plants are useful in reduction of complications of Alzheimer disease. In fact, these compounds were affective in reduction of stress oxidative and inflammation. They also had potential effect in reduction of A $\beta$  toxicity by abrogation of A $\beta$  generation and reduction of immature and full-length cellular holo-APP forms. Other their benefic effects were senile plaque reduction, inhibition of tau abnormal from, binding to iron and copper and reduction of their toxicity, dystrophic dendrites reduction, AMPK activation, DNA replication, up-regulation of genes related to cell cycle, regulation expression and phosphorylation of p53 increase of GSK-3 $\beta$  phosphorylation. These effects led to improvement of cognitive dysfunction and histological damages. Finally, we suggest that have to more focusing to natural product in order to treatment of Alzheimer disease and inhibition of its progression by to do further studies.

## Declarations

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