THE NEW ARMENIAN MEDICAL JOURNAL
Volume17 (2023), Issue 3 p.40-50

DOI: https://doi.org/10.56936/18290825-2023.17.3-40

THE EFFECT OF GALLIC ACID AS A PLANT POLYPHENOL COMPOUND ON OXIDATIVE STRESS INDUCED IN ALZHEIMER'S NEURODEGENERATIVE DISEASE

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Received 26.12.2022; accepted for printing 5.06.2023

Abstract

Alzheimer's disease as a neurodegenerative disorder is the most common reason of dementia. This disease is associated with many problems, including the inability to perform daily life activities and mood changes. The disease is defined by neuropathological signs including intracellular neurofibrillary tangles and extracellular amyloid beta plaques. Oxidative stress plays an important role in neurological diseases such as Alzheimer's, which can change the signaling pathways and change the function of the tau protein. Since there are many sources of reactive oxygen species in neurons, these cells create a system of antioxidant defense to protect themselves from free radical damage. Disruption of this antioxidant defense can make nerve cells vulnerable to oxidative damage. Natural compounds that have antioxidant properties can largely protect cells against these oxidative damages. One of these compounds is gallic acid, which is a phenolic compound and has a very strong antioxidant activity. This compound is found in plants such as oak bark, tea leaves, sumac, grapes, coriander, honey, berries, pomegranate, mango, and other fruits and vegetables. Gallic acid inhibits the accumulation of beta-amyloid plaques and reduces neurotoxicity, which prevents neurotoxicity and oxidative damage.

The aim of this study is to review the effect of gallic acid as a plant polyphenol compound on oxidative stress induced in Alzheimer's neurodegenerative disease.

Keywords: *polyphenol, gallic acid, antioxidants, oxidative stress, Alzheimer's disease.*

Introduction

Alzheimer's disease (AD) as a neurodegenerative disorder is the most prevalent reason of dementia. Neuropathologically, the disease is defined by the combined presence of extracellular amyloid beta (Aβ) plaques and intracellular neurofibrillary tangles. Amyloid beta plaques are deposited in the brain and the intracellular neurofibrillary composed of phosphorylated tau protein is shown excessively and abnormally. As a result of these pathways, synaptic- and neuro-toxicity occurs, leading to neuron loss and eventually brain atrophy [*Murphy M, LeVine H, 2010; Chen X, Mobley W, 2019*]. Alzheimer's disease is associated with neurodegeneration in brain areas involved in cognition such as the hippocampus, and entorhinal cortex, and brain areas involved in emotional behaviors

Cite This Article as:
Sani M., Hokmabadi M.E. (2023). The Effect Of Gallic Acid As A Plant Polyphenol Compound On Oxidative Stress Induced In Alzheimer's Neurodegenerative Disease; The New Armenian Medical Journal, vol.17(3), p 40-50; https://doi.org/10.56936/18290825-2023.17.3-40

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such as the amygdala, prefrontal cortex, and hypothalamus [*Rao Y et al., 2022*]. Therefore, the onset of this disorder is associated with the loss of episodic memory, and with the progress of the disease and the transition to the stage of dementia, in addition to memory deterioration, more severe symptoms appear [*Tarawneh R, Holtzman D, 2012; Jahn H, 2013*]. Also, language disorders, problem-solving, finding words, mood swings, reduced vision, and other cognitive skills are also symptoms of this disease that affect a person's life [*Atri A, 2019*]. The factors leading to the onset and uncontrolled progression of AD are not well understood to date. Alzheimer's disease is the result of a complex interaction between genetic and environmental factors [*Frisoni G et al., 2022*].

Examination of the brains of people with AD has reported a large amount of oxidative damage. Under normal conditions, damage caused by reactive oxygen species is controlled by a set of antioxidant systems. During pathological conditions, the balance of oxidant versus antioxidant changes and oxidative stress occurs, which causes the production of reactive oxygen species to exceed the antioxidant capacity of the cell [*Su B et al., 2008; Tönnies E, Trushina E, 2017*]. Oxidative stress plays an important role in neurological diseases such as AD, which can change the signaling pathways and change the function of the tau protein [*Su B et al., 2008*]. Neurons are highly dependent on reactions of oxidative phosphorylation in mitochondria to produce sources of energy. Their membranes comprise high concentrations of polyunsaturated fatty acids, which could act as substrates for reactions of lipid peroxidation. High concentrations of iron in its ion, which could catalyze the production of free radical, and lower glutathione concentrations, an endogenous antioxidant, make neurons highly vulnerable to free radical attack. Since exist several sources of reactive oxygen species in neuronal cells, these cells develop a system of antioxidant defense to keep themselves from free radical damage. This system comprises of enzymatic antioxidants including catalase, glutathione peroxidase, superoxide dismutase, non-enzymatic antioxidants such as glutathione, which balance the physiological reactive oxygen species (ROS) production with detoxification [*Ayala A et al., 2014; Ademowo O et al., 2017; Ionescu-Tucker A, Cotman C, 2021*].

Gallic acid or 3,4,5-trihydroxybenzoic acid as a phenolic complex has very robust antioxidant activity. This compound could be found both free and as part of hydrolysable tannins. The mentioned complex is broadly found in grapes, apples, green tea, black tea leaves, pineapples, pomegranates, nuts, and berries, and is presented in free form or as an ester compound. Gallic acid could ameliorate health of human through prevention or delaying of neurological disorders. This compound has strong antioxidant properties and ROS scavenging activities and can protect cells, tissues, and biological organs from damage caused by oxidative stress. Gallic acid is efficient vs. disorders related to nervous system such as Parkinson's disease, Alzheimer's disease, stroke, depression, and anxiety. Therefore, gallic acid could be considered as a worth nutritional compound [*Daglia M et al., 2014; Shabani S et al., 2020; Wianowska D, Olszowy-Tomczyk M, 2023*]. Based on the available evidence, gallic acid reduces the toxicity caused by Aβ in mouse neurons by preventing the release of Ca2+ from the endoplasmic reticulum into the cytoplasm and preventing the production of ROS and apoptosis. By elimination of ROS, inhibition of lipid peroxidation, and stimulation of the action of endogenous antioxidant factors, including superoxide dismutase, glutathione peroxidase, and catalase, this compound restores cerebellar oxidative stress and cognitive impairment caused by streptozotocin in mice. Also, in mice, gallic acid could reverse amnesia induced by scopolamine, possibly by preventing oxidative stress and reducing the activity of acetylcholinesterase enzyme in the brain [*Ogunlade B et al., 2022; Varesi A et al., 2023*].

The aim of this study is to review the effect of gallic acid as a plant polyphenol compound on oxidative stress induced in Alzheimer's neurodegenerative disease.

Alzheimer's disease: Alzheimer's disease is a progressive neurodegenerative disorder, which is

caused by the death of nerve cells, especially in the entorhinal cortex in the hippocampus. This neurological disorder usually affects people over 65 years old due to disorders in speech, memory, understanding, attention, judgment, and reasoning [*DeTure M, Dickson D, 2019; Cummings J, 2021*]. According to the level of cognitive impairment, this disorder is categorized into preclinical, mild, moderate, and late stages. Onset before age 65 (early onset) is uncommon and occurs in less than 10% of AD cases. An estimated 40 million people worldwide suffer from dementia, and this ratio is anticipated to be twice till 2050 [*Arvanitakis Z et al., 2019*]. The clinical stages of AD could be categorized into 4 stages. 1) Pre-symptomatic or pre-clinical phase: which could last numerous years. This phase is defined by loss of short-term memory and primary pathological alterations in the hippocampus and cortex, without functional damage in routine works and the lack of clinical symptoms of AD. 2) Mild or initial phase: in which several signs exist in patients, including problems in the patient's daily life with the loss of focus and memory and changes in mood and depression. 3) Intermediate phase: in which the disorder extents to the areas of the cerebral cortex, which leads to increased loss of memory with difficulty in knowing friends and family, and difficulty in speaking, writing, and reading. 4) Severe AD: this includes the extent of the disorder to the whole area of the cerebral cortex with the intense accumulation of neural plaques and neurofibrillary tangles, which leads to an advanced functional and cognitive disorder in which cases could not know their family in any way. In the final stages, the patient faces difficulty in swallowing food and excreting urine which eventually leads to death [*Caselli R, Reiman E, 2013; Dubois B et al., 2016; Vermunt L et al., 2019*].

Etiology and neuropathology of Alzheimer's disease: Aging is the main risk factor for AD. Depression, traumatic head injury, old age of parents, family history of dementia, elevated homocysteine level and existence of allele of APOE-e4, chronic infections of the central nervous system, cardiovascular and cerebrovascular disorder, obesity and diabetes increase the AD risk. People who have a brother or sister with late-onset of AD are 3 times more likely to develop AD than others [*Kalaria R et al., 2008; Dams-O'Connor K et al., 2016*]. Environmental factors such as smoking, air pollution, diet, and various metals can also increase the risk of developing AD [*Chin-Chan M et al., 2015; Antoniadou F et al., 2020*].

There are two kinds of neuropathological alterations in AD that offer evidence of disorder progression and signs, including 1) positive lesions characterized by the accumulation of neurofibrillary tangles, amyloid plaques, and dystrophic neurites; 2) negative lesions characterized by brain atrophy due to the loss of neurons, neuropil, and synapses. In addition, other factors including oxidative stress, neuroinflammation, and cholinergic neuron damage can cause neurodegeneration. Two important indicators for the diagnosis of AD are the accumulation of extracellular deposits of amyloid β plaque and neurofibrillary tangles of tau protein. Amyloid precursor protein (APP) as a membrane glycoprotein type 1 is produced in the endoplasmic reticulum and then is carried to the Golgi apparatus and finally located in the plasma membrane. This substance has a key role in a wide series of biological actions such as intracellular transport, neuronal growth, signaling, and neural homeostasis. Mature APP degrades after some time like all proteins [*Serrano-Pozo A et al., 2011; DeTure M, Dickson D, 2019*]. According to figure 1, there

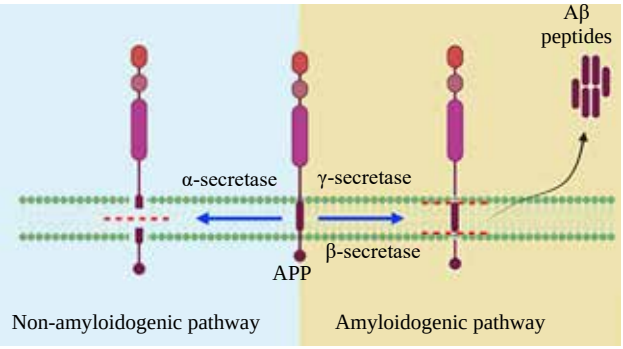

FIGURE 1. *Non-amyloidogenic and amyloidogenic pathways of amyloid precursor protein processing. In the non-amyloidogenic pathway, amyloid precursor protein is cleaved by α-secretases in a sequential manner, leading to the production of correct fragments by cleaving at the appropriate site. Amyloidogenic pathway involves sequential actions of β- and γ-secretases. This processing pathway results in the formation of β-amyloid peptides*

are two ways to break it down, named amyloidogenic and non-amyloidogenic. In the normal state (non-amyloidogenic pathway) and in the plasma membrane, by the sequential activity of α-secretase and γ-secretase, APP is cut from the appropriate place and becomes soluble pieces. But in AD (amyloidogenic pathway), inappropriate APP cleavage by β-secretase (the enzyme that breaks down the amyloid precursor protein, in amyloid beta), followed by γ-secretase cleavage, leads to the formation of toxic Aβ. Amyloid beta has a main role in neurotoxicity and neuronal function. Newly produced Aβ is either released into the extracellular region or deposited in connection with the plasmalemma and lipid structures of different brain regions, especially the hippocampus, and neocortex, and through its neurotoxic effects, it causes the development of AD [*Lichtenthaler S, Haass C, 2004; Castro M et al., 2019; Carare R et al., 2020*].

Tau is a hydrophilic protein encoded by the microtubule-associated protein tau gene on chromosome 17 [*Strang K et al., 2019*]. Tau proteins are very important for the physiological function of neurons, as they are responsible for microtubule polymerization, microtubule stabilization, and facilitating the transport of organelles and enzymes along the cytoskeleton. Tau is usually found in the cytosol and axon of neurons and has the ability to stabilize neuronal microtubules and is expressed in the central nervous system [*Mietelska-Porowska A et al., 2014*]. In normal physiological conditions, this protein is moderately phosphorylated, while in an abnormal condition, it is hyperphosphorylated and causes more accumulation of tau molecules in the vicinity of neurons [*Gong C, Iqbal K, 2008; Rajmohan R, Reddy P, 2017*]. These accumulated tau proteins eventually turn into neurofibrillary tangles and lead to neurodegenerative disorders such as AD. The reduced affinity of tau for microtubules contributes to neurotoxicity. The role of tau in microtubule stabilization and cytoskeleton strength and increased axonal transmission is undeniable. If this protein is destroyed, the cellular skeleton loses its strength, the signaling pathway is destroyed, and then the nerve cell is destroyed [*Medeiros R et al., 2011; Sinsky J et al., 2021*].

Oxidative stress and Alzheimer's disease: Oxidative stress is caused by an imbalance between the accumulation of ROS and its production, which acts as a double-edged sword in biological systems. In fact, in the state of oxidative stress, the imbalance in the redox condition causes excessive production of ROS and disrupts the functioning of the antioxidant system [*Sharifi-Rad M et al., 2020*]. The increase in ROS level is associated with oxidative damage of different cell parts. For instance, functional and structural disturbances of membrane-associated macromolecules including proteins and lipids have been observed in numerous parts of the brain in response to damage related to ROS. Oxidative stress related to AD also leads to changes in DNA structure with extensive oxidative damage to nucleic acids. Also, Aβ and Tau are affected by oxidative stress and play an important role in AD pathology through neurotoxicity and mitochondrial dysfunction [*Nita M, Grzybowski A, 2016; Juan C et al., 2021*]. The brain is exposed to oxidative damage due to high oxygen consumption, very low antioxidant levels, increased levels of unsaturated fatty acids, etc. ROS have been shown to cause cellular damage in aging and neurological disorders. Indeed, ROS-induced Aβ protein accumulation in AD causes lysosomal membrane degradation and ultimately contributes to neuronal death [*Garbarino V et al., 2015*]. Reactive oxygen species formation is significantly elevated via the electron transport system in mitochondria in aging and stressful situations, and when no effective antioxidant system is accessible, it causes the AD risk. Mitochondria act as a source of toxic ROS, and therefore dysfunction of mitochondria and oxidative stress are main in neurodegenerative diseases, especially AD [*Dai D et al., 2014; Huang W et al., 2016*].

Antioxidant compounds: Antioxidants are compounds that prevent or delay the oxidation of oxidizable substrates in cell. Different antioxidants apply their influences via scavenging ROS. Oxidation prevention is an essential process in all organisms and cells, because the reduction of antioxidant protection might result in cell apoptosis, cyto-

toxicity, mutagenesis, or carcinogenesis. The application of antioxidant complexes in the diet as a kind of treatment for these disorders is suitable, but it is limited due to the difficulties in reaching the appropriate level in the brain. Antioxidants with natural origin such as polyphenols exert neuroprotective influences by interacting with transition metals, scavenging free radicals, modulating enzyme activity, and affecting gene expression and intracellular signaling pathways [*Matés J, 2000; Lobo V et al., 2010*]. Diets rich in antioxidants have a key protective role vs. several pathologies. Fruits and vegetables are the main sources of these molecules and are correlated with lower risk of heart disease, malignancy, neurological disease, and stroke. These diseases are difficult to treat with synthetic complexes because of their capability to origin cancer and cytotoxicity. Then, treatment with natural antioxidants including polyphenols in food supplements or diet has developed a good alternative [*Knasmüller S et al., 2008*].

Polyphenols: Polyphenols are secondary metabolites created by higher plants that have several main roles in physiology of plant and have possible health features in human organisms. They are chiefly known as antioxidant, anti-allergenic, anti-inflammatory, anti-cancer, anti-hypertensive, and anti-microbial. Their key food sources are fruits and herbal drinks including juice, tea, and coffee. Other foods such as vegetables, grains, chocolate, and dry beans also play a role in polyphenol absorption. Most likely, cells respond to polyphenols chiefly via direct interaction with enzymes or receptors involved in signal transduction, which might lead to a change in oxidation state and also trigger a sequences of redox responses [*Pandey K, Rizvi S, 2009; Daglia M, 2012*]. In terms of chemical structure, many diverse molecules are formed with polyphenol structures and are classified into two categories, non-flavonoids and flavonoids. The oxidation condition of the central pyran ring of polyphenols, flavonoids could be divided into several groups such as anthocyanidins, flavones, flavonols, flavanols, as well as isoflavones. Non-flavonoid groups are phenolic acids, which can be categorized into derivatives of benzoic acid, gallic acid and protocatechuic acid, and derivatives of cinnamic acid, which are mainly composed of coumaric, caffeic acid, and ferulic acids [*Pandey K, Rizvi S, 2009; Mutha R et al., 2021*].

Gallic acid: Gallic acid or 3,4,5-trihydroxybenzoic acid and their derivatives are biologically active complexes that are broadly found in plants. Gallic acid is one of the chelating units that cause the formation of highly stable complexes with ferrous iron [*Fernandes F, Salgado H, 2016*]. Gallic acid is stable over a wide range of pH. The production of ester and amide bonds of synthetic gallic acid derivatives is to increase the antioxidant quality of Gallovil group [*Queiroz M et al., 2019*]. Gallic acid can be produced by acid, alkaline, and enzymatic hydrolysis, and used as a strong antioxidant in emulsion or lipid systems [*Choubey S et al., 2018*]. High amounts of hydroxyl group cause high antioxidant activity as hydrogen and electron donating units. Gallic acid is available in both free and ester forms and in salt forms. The salt form of gallic acid is called gallate and is part of the ellagitannin tannin structure, which includes hydrolyzable tannin [*da Rosa C et al., 2013*]. Gallic acid is unstable at high temperatures and in the existence of light and oxygen. The encapsulation of gallic acid causes the durability and biological activity of this compound. The degree of protection obtained by encapsulation is determined by the choice of encapsulation method [*Quiles-Carrillo L et al., 2019*].

Free radicals that arise during cell metabolism cause many disorders including cardiovascular diseases, neurological diseases, cancer, diabetes, and osteoporosis. Gallate esters are antioxidant units against hydroxyl radicals, azide, and superoxide radicals and prevent atherosclerosis [*Pham-Huy L et al., 2008*]. Cell membranes are one of the target sites for free radicals. The participation of gallic acid with phospholipids in organic solutions improves the antioxidant potential of gallic acid by increasing its biological availability [*Badhani B et al., 2015*]. Gallic acid stops the production of mutagenic compounds. Active oxygen species and active nitrogen species play an essential role in stimulating and initiating the process of nephron toxicity and kidney damage. Natural antioxidants such as gallic

acid can eliminate these effects in the kidneys. Gallic acid prevents the toxicity of nephron cells by free radicals via neutralizing them. The protective effect of gallic acid on the nephron is related to the neutralizing potential of nitric acid and the neutralizing effect of hydroxyl radicals [*Ratliff B et al., 2016; Ashkar F et al., 2022*]. Antioxidants act not only as antioxidants but also as moderators of inflammation symptoms. Many studies on the relationship between antioxidant and anti-inflammatory activity have suggested that polyphenols can reduce inflammation by a number of reduction mechanisms including superoxide anion scavenging. Polyphenols are also effective in the treatment of neurological diseases. In fact, polyphenols neutralize free radicals that stimulate the oxidation of lipids in the cell membrane and cause the neuron to fail and eventually die. Antioxidant and anti-inflammatory molecules deal with some neuron diseases such as Alzheimer's and Parkinson's [*Luo J et al., 2021; Mucha P et al., 2021*].

Antioxidant properties of gallic acid in Alzheimer's disease: Gallic acid can have antioxidant and peroxidative properties [*Gao J et al., 2019*]. Plant polyphenols such as ferulic acid, and caffeic acid have both antioxidant and peroxidative properties [*Pandey K, Rizvi S, 2009*]. The ability of polyphenols to act as antioxidant and peroxide compounds under living and non-living systems depend on factors such as concentration, structure, tested system and the substance to be protected. Many antioxidants may act as peroxides under certain conditions. This usually involves their reaction with transition metal ions. They can convert Fe3+ and Cu2+ into Fe2+ and Cu+. This action provokes oxidative damage under certain conditions. Oxidized phenols (such as quinone and semiquinone) are formed from phenolic compounds during redox reactions. It should be kept in mind that strong antioxidants can show peroxidative behavior and cause oxidative damage to cells [*Lobo V et al., 2010; Costa M et al., 2021*]. For example, gallic acid and epigallocatechin gallate have strong antioxidant activity in the degradation of deoxyribose during the reduction of Fe3+ to Fe2+ [*Cheng Z et al., 2003*]. The antioxidant properties of gallic acid are shown in figure 2.

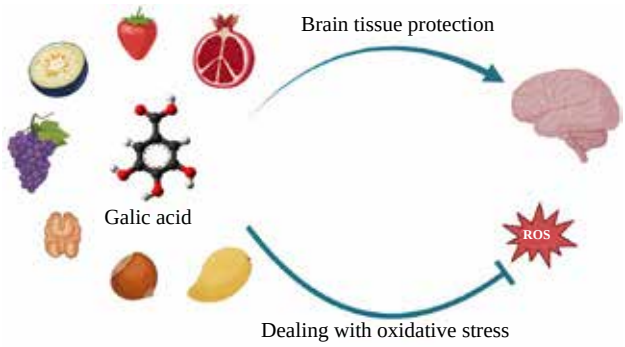

Figure 2. *Garlic acid sources and brain protection. Garlic acid exists in many natural sources including strawberry, pomegranate, blueberry, grape, walnut, hazelnut and mango. This compound overcomes oxidative stress and causes the preservation of brain tissue in Alzheimer's disease*

As mentioned, oxidative stress is responsible for a variety of degenerative disorders, such as AD, and gallic acid, with its antioxidant properties, reduces oxidative stress and can help reduce Alzheimer's symptoms [*Collins A et al., 2022*]. Gallic acid stabilizes the acetylation of nuclear factor kappa B and reduces the generation of cytokines in microglia and protects neurons against Aβ-induced neurotoxicity and also reduces inflammation [*Kim M et al., 2011*]. Gallic acid reduces the release of calcium ions and ROS in PC12 cells [*Huang H et al., 2012*]. In damaged rats, memory could be improved by oral administration of gallic acid [*Hajipour S et al., 2016*]. Gallic acid has received much attention because of its capability to absorb ROS, including hydroxyl radicals, hydrogen peroxide, superoxide anions, and antitumor activity [*Le Thi P et al., 2020*]. In addition, gallic acid has neuroprotective influences vs. Aβ (reducing the size of Aβ plaques in the brain), lead nitrate, and sodium fluoride [*Shabani S et al., 2020*]. Indeed, in vitro analysis showed that gallic acid interferes with Aβ1-42 aggregation and reduces neurotoxicity, which prevents neurotoxicity and oxidative damage [*Yu M et al., 2019*]. Overactivity of the acetylcholinesterase enzyme might result in acetylcholine deficit and impairment of memory. Gallic acid could improve learning and memory via reducing activity of acetylcholinesterase enzyme and increasing acetylcholine levels.

CONCLUSION

Antioxidants are substances that, in low concentrations, can reduce or prevent the damage caused by free radicals by absorbing and removing them. Humans get antioxidant supplements directly from fresh fruits and vegetables. Fruits and vegetables contain a lot of flavonoids and antioxidant supplements that help protect against various types of diseases.

In the last few decades, human lifestyle and perspectives on nutrition are changing, and therefore, packaged and ready-to-eat foods are highly welcomed. Therefore, in order to maintain human health, there is a need for special protective agents called antioxidants. Many plants and species such as rosemary, thyme, oregano, sage, basil, pepper, tea, grapes, cloves, and cinnamon contain antioxidant components and transfer these properties to the entire composition. Gallic acid and its derivatives are a group of biomolecules found in plants such as oak bark, tea leaves, sumac, grapes, coriander, honey, berries, pomegranate, mango, and other fruits and vegetables. These solid phenolic compounds have properties such as antioxidant properties that are potentially beneficial for health. Gallic acids have potential antioxidant properties and prevent oxidation by stopping the reaction of free radicals. Oxidative stress is responsible for a variety of degenerative diseases, including Alzheimer's, and gallic acid, with its antioxidant properties, reduces oxidative stress and can help reduce Alzheimer's symptoms. With its antioxidant properties, gallic acid reduces the damaging effects of Alzheimer's in nerve cells by interfering with some cellular cascades.

Therefore, this substance can promise a suitable herbal treatment for Alzheimer's neurodegenerative disease.

REFERENCES

1. *Ademowo OS, Dias HK, Burton DG, Griffiths HR (2017).* Lipid (per) oxidation in mitochondria: an emerging target in the ageing process? Biogerontology, 18(6): 859-879. https://doi.org/10.1007/s10522-017-9710-z
2. *Antoniadou F, Papamitsou T, Kavvadas D, Kapoukranidou D, Sioga A, Papaliagkas V (2020).* Toxic environmental factors and their association with the development of dementia: A mini review on heavy metals and ambient particulate matter. Materia Socio-Medica, 32(4): 299. doi: 10.5455/msm.2020.32.299-306
3. *Arvanitakis Z, Shah RC, Bennett DA (2019).* Diagnosis and management of dementia. JAMA, 322(16): 1589-1599. doi:10.1001/jama.2019.4782
4. *Ashkar F, Bhullar KS, Wu J (2022).* The effect of polyphenols on kidney disease: Targeting mitochondria. Nutrients, 14(15): 3115. https://doi.org/10.3390/nu14153115
5. *Atri A (2019).* The Alzheimer's disease clinical spectrum: diagnosis and management. Medical Clinics, 103(2): 263-293. https://doi.org/10.1016/j.mcna.2018.10.009
6. *Ayala A, Muñoz MF, Argüelles S (2014).* Lipid peroxidation: production, metabolism, and signaling mechanisms of malondialdehyde and 4-hydroxy-2-nonenal. Oxidative Medicine and Cellular Longevity, 2014. https://doi.org/10.1155/2014/360438
7. *Badhani B, Sharma N, Kakkar R (2015).* Gallic acid: A versatile antioxidant with promising therapeutic and industrial applications. Rsc Advances, 5(35): 27540-27557. DOI: 10.1039/C5RA01911G
8. *Carare RO, Aldea R, Agarwal N, Bacskai BJ, Bechman I., et al (2020).* Clearance of interstitial fluid (ISF) and CSF (CLIC) group—part of Vascular Professional Interest Area (PIA) Cerebrovascular disease and the failure of elimination of Amyloid-β from the brain and retina with age and Alzheimer's disease-Opportunities for Therapy. Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring. 12(1): e12053.

9. *Caselli RJ, Reiman EM (2013).* Characterizing the preclinical stages of Alzheimer's disease and the prospect of presymptomatic intervention. Journal of Alzheimer's Disease, 33(s1): S405-S416. DOI: 10.3233/JAD-2012-129026

10. *Castro MA, Hadziselimovic A, Sanders CR (2019).* The vexing complexity of the amyloidogenic pathway. Protein Science, 28(7): 1177-1193. https://doi.org/10.1002/pro.3606

11. *Chen XQ, Mobley WC (2019).* Alzheimer disease pathogenesis: insights from molecular and cellular biology studies of oligomeric Aβ and tau species. Frontiers in Neuroscience, 13: 659. https://doi.org/10.3389/fnins.2019.00659

12. *Cheng Z, Li Y, Chang W (2003).* Kinetic deoxyribose degradation assay and its application in assessing the antioxidant activities of phenolic compounds in a Fenton-type reaction system. Analytica Chimica Acta, 478(1): 129-137. https://doi.org/10.1016/S0003-2670(02)01435-6

13. *Chin-Chan M, Navarro-Yepes J, Quintanilla-Vega B (2015).* Environmental pollutants as risk factors for neurodegenerative disorders: Alzheimer and Parkinson diseases. Frontiers in cellular neuroscience, 9: 124. https://doi.org/10.3389/fncel.2015.00124

14. *Choubey S, Goyal S, Varughese LR, Kumar V, Sharma AK, Beniwal V (2018).* Probing gallic acid for its broad spectrum applications. Mini reviews in medicinal chemistry, 18(15): 1283-1293. https://doi.org/10.2174/1389557518666180330114010

15. *Collins AE, Saleh TM, Kalisch BE (2022).* Naturally occurring antioxidant therapy in Alzheimer's disease. Antioxidants, 11(2): 213. https://doi.org/10.3390/antiox11020213

16. *Colovic MB, Krstic DZ, Lazarevic-Pasti TD, Bondzic AM, Vasic VM (2013).* Acetylcholinesterase inhibitors: pharmacology and toxicology. Current Neuropharmacology, 11(3): 315-335.

17. *Costa M, Sezgin-Bayindir Z, Losada-Barreiro S, Paiva-Martins F, Saso L, Bravo-Díaz C (2021).* Polyphenols as antioxidants for extending food shelf-life and in the prevention of health diseases: Encapsulation and interfacial phenomena. Biomedicines, 9(12): 1909. https://doi.org/10.3390/biomedicines9121909

18. *Cummings J (2021).* The role of neuropsychiatric symptoms in research diagnostic criteria for neurodegenerative diseases. The American Journal of Geriatric Psychiatry, 29(4): 375-383. https://doi.org/10.1016/j.jagp.2020.07.011

19. *Da Rosa CG, Borges CD, Zambiazi RC, Nunes MR, Benvenutti EV., et al (2013).* Microencapsulation of gallic acid in chitosan, β-cyclodextrin and xanthan. Industrial Crops and Products, 46: 138-146. https://doi.org/10.1016/j.indcrop.2012.12.053

20. *Daglia M (2012).* Polyphenols as antimicrobial agents. Current Opinion Biotechnology, 23(2): 174-181. https://doi.org/10.1016/j.copbio.2011.08.007

21. *Daglia M, Di Lorenzo A, F Nabavi S, S Talas Z, M Nabavi S (2014).* Polyphenols: well beyond the antioxidant capacity: gallic acid and related compounds as neuroprotective agents: you are what you eat! Current Pharmaceutical Biotechnology, 15(4): 362-372.

22. *Dai DF, Chiao YA, Marcinek DJ, Szeto HH, Rabinovitch PS (2014).* Mitochondrial oxidative stress in aging and healthspan. Longevity & Healthspan, 3(1): 1-22.

23. *Dams-O'Connor K, Guetta G, Hahn-Ketter AE, Fedor A (2016).* Traumatic brain injury as a risk factor for Alzheimer's disease: current knowledge and future directions. Neurodegenerative Disease Management, 6(5): 417-429. https://doi.org/10.2217/nmt-2016-0017

24. *DeTure MA, Dickson DW (2019).* The neuropathological diagnosis of Alzheimer's disease. Molecular Neurodegeneration, 14(1): 1-8.

25. *Dubois B, Hampel H, Feldman HH, Scheltens P, Aisen P., et al (2016).* Preclinical Alzheimer's disease: definition, natural history, and diagnostic criteria. Alzheimer's & Dementia, 12(3): 292-323. https://doi.org/10.1016/j.jalz.2016.02.002

26. *Fernandes FH, Salgado HR (2016).* Gallic acid: review of the methods of determination and quantification. Critical Reviews in Ana-

lytical Chemistry. 46(3): 257-265 https://doi.org/10.1080/10408347.2015.1095064

27. *Frisoni GB, Altomare D, Thal DR, Ribaldi F, van der Kant R., et al (2022).* The probabilistic model of Alzheimer disease: the amyloid hypothesis revised. Nature Reviews Neuroscience, 23(1): 53-66. https://doi.org/10.1038/s41583-021-00533-w

28. *Gao J, Hu J, Hu D, Yang X (2019).* A role of gallic acid in oxidative damage diseases: A comprehensive review. Natural Product Communications, 14(8): 1934578X19874174. https://doi.org/10.1177/1934578X19874174

29. *Garbarino VR, Orr ME, Rodriguez KA, Buffenstein R (2015).* Mechanisms of oxidative stress resistance in the brain: lessons learned from hypoxia tolerant extremophilic vertebrates. Archives of Biochemistry and Biophysics, 576: 8-16. https://doi.org/10.1016/j.abb.2015.01.029

30. *Gong CX, Iqbal K (2008).* Hyperphosphorylation of microtubule-associated protein tau: a promising therapeutic target for Alzheimer disease. Current Medicinal Chemistry, 15(23): 2321-2328. https://doi.org/10.2174/092986708785909111

31. *Hajipour S, Sarkaki A, Farbood Y, Eidi A, Mortazavi P, Valizadeh Z (2016).* Effect of gallic acid on dementia type of Alzheimer disease in rats: electrophysiological and histological studies. Basic and Clinical Neuroscience, 7(2): 97-106. doi: 10.15412/J.BCN.03070203

32. *Huang HL, Lin CC, Jeng KC, Yao PW, Chuang LT., et al (2012).* Fresh green tea and gallic acid ameliorate oxidative stress in kainic acid-induced status epilepticus. Journal of Agricultural and Food Chemistry, 60(9): 2328-2336. https://doi.org/10.1021/jf203709q

33. *Huang WJ, Zhang XI, Chen WW (2016).* Role of oxidative stress in Alzheimer's disease. Biomedical Reports, 4(5): 519-522. https://doi.org/10.3892/br.2016.630

34. *Ionescu-Tucker A, Cotman CW (2021).* Emerging roles of oxidative stress in brain aging and Alzheimer's disease. Neurobiology of Aging, 107: 86-95. https://doi.org/10.1016/j.neurobiolaging.2021.07.014

35. *Jahn H (2013).* Memory loss in Alzheimer's disease. Dialogues Clinical Neuroscience, 15(4): 445-454. https://doi.org/10.31887/DCNS.2013.15.4/hjahn

36. *Juan CA, Pérez de la Lastra JM, Plou FJ, Pérez-Lebeña E (2021).* The chemistry of reactive oxygen species (ROS) revisited: outlining their role in biological macromolecules (DNA, lipids and proteins) and induced pathologies. International Journal of Molecular Sciences, 22(9): 4642. https://doi.org/10.3390/ijms22094642

37. *Kalaria RN, Maestre GE, Arizaga R, Friedland RP, Galasko D., et al (2008).* Alzheimer's disease and vascular dementia in developing countries: prevalence, management, and risk factors. The Lancet Neurology, 7(9): 812-826. https://doi.org/10.1016/S1474-4422(08)70169-8

38. *Kim MJ, Seong AR, Yoo JY, Jin CH, Lee YH., et al (2011).* Gallic acid, a histone acetyltransferase inhibitor, suppresses β-amyloid neurotoxicity by inhibiting microglial-mediated neuroinflammation. Molecular nutrition & Food Research, 55(12): 1798-1808. https://doi.org/10.1002/mnfr.201100262

39. *Knasmüller S, Nersesyan A, Mišík M, Gerner C, Mikulits W., et al (2008).* Use of conventional and-omics based methods for health claims of dietary antioxidants: a critical overview. British Journal of Nutrition, 99(E-S1): ES3-E52. https://doi.org/10.1017/S0007114508965752

40. *Le Thi P, Lee Y, Tran DL, Thi TT, Kang JI., et al (2020).* In situ forming and reactive oxygen species-scavenging gelatin hydrogels for enhancing wound healing efficacy. Acta Biomaterialia, 103: 142-152. https://doi.org/10.1016/j.actbio.2019.12.009

41. *Lichtenthaler SF, Haass C (2004).* Amyloid at the cutting edge: activation of α-secretase prevents amyloidogenesis in an Alzheimer disease mouse model. The Journal of Clinical Investigation, 113(10): 1384-1387. doi: 10.1172/JCI21746

42. *Lobo V, Patil A, Phatak A, Chandra N (2010).* Free radicals, antioxidants and functional foods: Impact on human health. Phar-

macognosy Reviews, 4(8): 118-126. doi: 10.4103/0973-7847.70902

43. *Luo J, Si H, Jia Z, Liu D (2021).* Dietary anti-aging polyphenols and potential mechanisms. Antioxidants, 10(2): 283. https://doi.org/10.3390/antiox10020283

44. *Matés JM (2000).* Effects of antioxidant enzymes in the molecular control of reactive oxygen species toxicology. Toxicology, 153(1-3): 83-104. https://doi.org/10.1016/S0300-483X(00)00306-1

45. *Medeiros R, Baglietto-Vargas D, LaFerla FM (2011).* The role of tau in Alzheimer's disease and related disorders. CNS Neuroscience & Therapeutics, 17(5): 514-524. https://doi.org/10.1111/j.1755-5949.2010.00177.x

46. *Mietelska-Porowska A, Wasik U, Goras M, Filipek A, Niewiadomska G (2014).* Tau protein modifications and interactions: their role in function and dysfunction. International Journal of Molecular Sciences, 15(3): 4671-4713. https://doi.org/10.3390/ijms15034671

47. *Mucha P, Skoczyńska A, Małecka M, Hikisz P, Budzisz E (2021).* Overview of the antioxidant and anti-inflammatory activities of selected plant compounds and their metal ions complexes. Molecules, 26(16): 4886. https://doi.org/10.3390/molecules26164886

48. *Murphy MP, LeVine H (2010).* Alzheimer's disease and the amyloid-beta peptide. Journal of Alzheimers Diseases, 19(1): 311-323.

49. *Mutha RE, Tatiya AU, Surana SJ (2021).* Flavonoids as natural phenolic compounds and their role in therapeutics: An overview. Future Journal of Pharmaceutical Sciences, 7: 1-3. https://doi.org/10.1186/s43094-020-00161-8

50. *Nita M, Grzybowski A (2016).* The role of the reactive oxygen species and oxidative stress in the pathomechanism of the age-related ocular diseases and other pathologies of the anterior and posterior eye segments in adults. Oxidative Medicine and Cellular Longevity. https://doi.org/10.1155/2016/3164734

51. *Ogunlade B, Adelakun SA, Agie JA (2022).* Nutritional supplementation of gallic acid ameliorates Alzheimer-type hippocampal neurodegeneration and cognitive impairment induced by aluminum chloride exposure in adult Wistar rats. Drug and Chemical Toxicology, 45(2): 651-662. https://doi.org/10.1080/01480545.2020.1754849

52. *Pandey KB, Rizvi SI (2009).* Plant polyphenols as dietary antioxidants in human health and disease. Oxidative Medicine and Cellular Longevity, 2: 270-278. https://doi.org/10.4161/oxim.2.5.9498

53. *Pham-Huy LA, He H, Pham-Huy C (2008).* Free radicals, antioxidants in disease and health. International journal of biomedical science: IJBS, 4(2): 89.

54. *Queiroz MF, Sabry DA, Sassaki GL, Rocha HA, Costa LS (2019).* Gallic acid-dextran conjugate: Green synthesis of a novel antioxidant molecule. Antioxidants, 8(10): 478. https://doi.org/10.3390/antiox8100478

55. *Quiles-Carrillo L, Montava-Jordà S, Boronat T, Sammon C, Balart R, Torres-Giner S (2019).* On the use of gallic acid as a potential natural antioxidant and ultraviolet light stabilizer in cast-extruded bio-based high-density polyethylene films. Polymers, 12(1): 31. https://doi.org/10.3390/polym12010031

56. *Rajmohan R, Reddy PH (2017).* Amyloid-beta and phosphorylated tau accumulations cause abnormalities at synapses of Alzheimer's disease neurons. Journal of Alzheimer's Disease, 57(4): 975-999.

57. *Rao YL, Ganaraja B, Murlimanju BV, Joy T, Krishnamurthy A, Agrawal A (2022).* Hippocampus and its involvement in Alzheimer's disease: a review. 3 Biotech, 12(2): 55. https://doi.org/10.1007/s13205-022-03123-4

58. *Ratliff BB, Abdulmahdi W, Pawar R, Wolin MS (2016).* Oxidant mechanisms in renal injury and disease. Antioxidants & Redox Signaling, 25(3): 119-146. https://doi.org/10.1089/ars.2016.6665

59. *Serrano-Pozo A, Frosch MP, Masliah E, Hyman BT (2011).* Neuropathological alterations in Alzheimer disease. Cold Spring Harbor Perspectives in Medicine, 1(1): a006189.

60. *Shabani S, Rabiei Z, Amini-Khoei H (2020).* Exploring the multifaceted neuroprotective actions of gallic acid: A review. International Journal of Food Properties 23(1): 736-752. https://doi.org/10.1080/10942912.2020.1753769

61. *Sharifi-Rad M, Anil Kumar NV, Zucca P, Varoni EM, Dini L., et al (2020).* Lifestyle, oxidative stress, and antioxidants: Back and forth in the pathophysiology of chronic diseases. Frontiers in Physiology, 11: 694. https://doi.org/10.3389/fphys.2020.00694

62. *Sinsky J, Pichlerova K, Hanes J (2021).* Tau protein interaction partners and their roles in Alzheimer's disease and other tauopathies. International Journal of Molecular Sciences, 22(17): 9207. https://doi.org/10.3390/ijms22179207

63. *Strang KH, Golde TE, Giasson BI (2019).* MAPT mutations, tauopathy, and mechanisms of neurodegeneration. Laboratory investigation, 99(7): 912-928. https://doi.org/10.1038/s41374-019-0197-x

64. *Su B, Wang X, Nunomura A, Moreira PI, Lee HG., et al (2008).* Oxidative stress signaling in Alzheimer's disease. Current Alzheimer Research, 5(6): 525-532. https://doi.org/10.2174/156720508786898451

65. *Tarawneh R, Holtzman DM (2012).* The clinical problem of symptomatic Alzheimer disease and mild cognitive impairment. Cold Spring Harbor Perspectives in Medicine, 2(5). doi: 10.1101/cshperspect.a006148

66. *Tönnies E, Trushina E (2017).* Oxidative stress, synaptic dysfunction, and Alzheimer's disease. Journal of Alzheimer's Disease, 57(4): 1105-1121.

67. *Varesi A, Campagnoli LI, Carrara A, Pola I, Floris E., et al (2023).* Non-enzymatic antioxidants against Alzheimer's disease: prevention, diagnosis and therapy. Antioxidants, 12(1): 180. https://doi.org/10.3390/antiox12010180

68. *Vermunt L, Sikkes SA, Van Den Hout A, Handels R, Bos I., et al (2019).* Duration of preclinical, prodromal, and dementia stages of Alzheimer's disease in relation to age, sex, and APOE genotype. Alzheimer's & Dementia, 15(7): 888-898. https://doi.org/10.1016/j.jalz.2019.04.001

69. *Wianowska D, Olszowy-Tomczyk M (2023).* A concise profile of gallic acid—From its natural sources through biological properties and chemical methods of determination. Molecules, 28(3): 1186. https://doi.org/10.3390/molecules28031186

70. *Yu M, Chen X, Liu J, Ma Q, Zhuo Z., et al (2019).* Gallic acid disruption of Aβ1–42 aggregation rescues cognitive decline of APP/PS1 double transgenic mouse. Neurobiology of Disease, 124: 67-80. https://doi.org/10.1016/j.nbd.2018.11.009

THE NEW ARMENIAN MEDICAL JOURNAL
Volume17 (2023). Issue 3

CONTENTS

THE NEW ARMENIAN MEDICAL JOURNAL

Volume17 (2023). Issue 3

The Journal is founded by
Yerevan State Medical
University after M. Heratsi.

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Our journal is registered in the databases of Scopus, EBSCO and Thomson Reuters (in the registration process)

SCOPUS EBSCO
REUTERS

Copy editor: Tatevik R. Movsisyan

Printed in "LAS Print" LLC
Director: Suren A. Simonyan
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