# Phenolic Antioxidants as Drugs for Alzheimer's Disease: Oxidative Stress and Selectivity

**Peter Kovacic[1]* and Wil Weston[2]**

[1]Department of Chemistry and Biochemistry, San Diego State University, USA

[2]Library and Information Access, San Diego State University, USA

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**\*Corresponding author:** Peter Kovacic, Department of Chemistry and Biochemistry, San Diego State University, USA,
Email: pkovacic@mail.sdsu.edu

### Abstract

Oxidative stress (OS) is a well-recognized feature of Alzheimer's disease. However, even up to the present time, there is controversy and conflicting results concerning the role of antioxidants (AO). This review provides evidence for the beneficial influence of phenols and phenolic ethers as AOs. Other mechanisms were advanced for these drugs previously; however, this report adds validity to the positive influence of AOs on Alzheimer's disease. An important aspect to be recognized is the variability of action with a class based on competing pathways. The AOs involved are the following: curcumin, seasamol, rivastigmine, galantamine, donepezil, and piperine.

**Abbreviations:** AGE: Advanced Glycation End Products; OS: Oxidative Stress; ET: Electron Transfer; ROS: Reactive Oxygen Species; AO: Antioxidant; 4-HNE: 4-hydroxynonenal; RNS: Reactive Nitrogen Species

**Keywords:** Phenolic antioxidants; Alzheimer's disease; Oxidative stress

## Introduction

Two of the pathological features of Alzheimer's disease are senile plaques (or neuritic plaques) and neurofibrillary tangles, including amyloid–β–peptides [1]. Suggested mechanisms for formation of these proteins include oxidation by reactive oxygen species (ROS) and reactive nitrogen species (RNS), advanced glycation end products (AGE) formation via oxidation and metal compound involvement, where AOs may have a significant impact. A recent review addressed AGE based on oxidative events [2] in which quinones comprise an important class of electron transfer (ET) agents that generate ROS and OS. The ET agents are often formed by oxidation of phenolic compounds that make up part of drugs and physiologically active species. The phenolics are the focus of this commentary.

## Discussion

There is early literature before 2000 for elevated levels of oxidative damage in vivo in Alzheimer's disease. The evidence involves elevations in 8-OH-dG, other DNA based oxidation products, protein carbonyls, nitrotyrosine,4-hydroxynonenal (4-HNE), and other products from lipid peroxidation. Notably, 4-HNE is quite toxic to neurons and senile plaques are involved in oxidative insult. The iron in senile plaques may facilitate oxidative damage via ET suggesting that inflammation from plaques could play a role involving ROS and RNS generation [3].

The importance of OS in Alzheimer's disease has been well established [4] and is generally accepted. However, there remains uncertainty and debate over the role of AOs. The 2015 title raises the question, "should we keep trying antioxidant therapies?" [4] A study with vitamins E and C in Alzheimer's disease patients revealed no differences in clinical outcomes. No difference in clinical progression was seen with the AO ginkgo biloba biloba or with estrogen in Alzheimer's disease patients. The possible reasons for lack of beneficial effects were discussed; however, the study's conclusion was that more studies were needed to resolve the conflicting aspects. In other investigations, a current 2017 report stated that "Oxidative stress is an established dementia pathway, but it is unknown if the use of AO supplements can prevent dementia", with a focus on Alzheimer's disease [5]. Another earlier investigation stated that there is "evidence for the benefits of AOs based on therapeutic intervention in dementia are inconsistent" with reference to Alzheimer's disease [6].

This report adds support to the notion that AOs can play an important role in Alzheimer's disease. However, it should

be emphasized that selectivity is an important factor in determining the outcome in which various factors are involved. This report deals with phenolics and/or phenolic ethers as AO in Alzheimer's disease. The class is well known to possess AO properties. However, prior literature pays little attention to this aspect, but instead emphasizes enzyme inhibition as the mode of action. These AO compounds comprise: curcumin, seasamol, rivastigmine, galantamine, donepezil, and piperine.

### a.   Curcumin
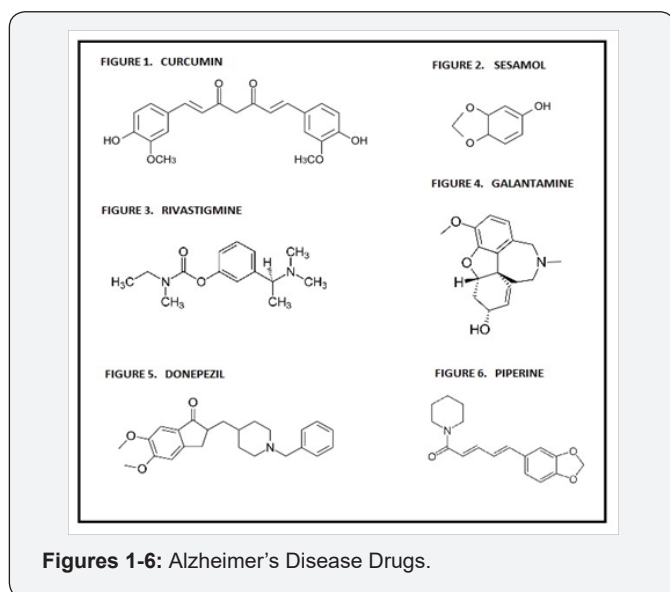


**Figures 1-6:** Alzheimer's Disease Drugs.

Curcumin (Figure 1), a spice, is a phenol type and phenolic ether. The diketone can undergo tautomerism to the keto-enol form. The compound displays a wide spectrum of drug and physiological activities, including AO action [7]. In a 2008 study, memory in people with Alzheimer's disease was improved [8]; which was later supported in a 2010 review noting this memory property as well [9]. Additionally, recent literature has indicated the potential of this substance in the treatment of Alzheimer's disease. Furthermore, curcumin inhibits amyloid β protein, amyloid β aggregation, deposition, and oligomerization. Improvement in animal models was noted. These reports indicate that curcumin may be a primary candidate for Alzheimer's disease therapy. Lastly, another study in 2005demonstrated AO, anti-inflammatory and anti-amyloid activity in the aspects of Alzheimer's disease [10]. The AO aspect is particularly relevant, placing this structure in accord with ROS-OS-AO approach.

### b.   Sesamol

Sesamol (Figure 2), present in sesame, has the common phenolic and phenolic ether structures. Its AO properties have been known for some time [11,12]. Various physiological responses are elicited including antifungal which was attributed to signaling [13,14]. Neuroinflammation appears to be involved in a number of neurodegenerative disorders reported, including Alzheimer's disease. Sesamol is reported to prevent inflammation induced memory impairment [15] and lessens

inflammation in diabetic neuropathy. Moreover, modulation of the oxidative NO pathway by the phenolic prevents cognitive deficits in an Alzheimer's disease animal model. Again, these properties fit the ROS-OS-AO mechanistic scheme.

### c.   Rivastigmine

Rivastigmine (Figure 3), a phenolic ester is of interest as an agent for the treatment of mild to moderate Alzheimer's disease [16]. Esterases are common enzymes that catalyze the hydrolysis of esters. The hydrolytic cleavage can also be achieved by catalysis involving a proton. The result is the generation of an AO phenol. In addition, the compound is an acetyl cholinesterase inhibitor [17]. In this case, rivastigmine is in accordance with ROS – OS –AO and is achieved through its proposed phenolic metabolite.

### d.   Galantamine

Galantamine (Figure 4), a plant alkaloid phenolic ester, is used for the treatment of mild to moderate Alzheimer's disease, in addition to other memory disorders [18]. Along with others of this phenolic class, it is an acetylcholinesterase inhibitor [19]. This appears to be another case in which a metabolite plays a key role. Demethylation would yield an AO derivative, which is a widespread structure in this class. Dealkylation of phenolic ethers has been treated previously; for instance in the case of etoposide [20].

### e.   Donepezil

Donepezil (Figure 5), a phenolic diether, is used as the standard palliative treatment of Alzheimer's disease [21]. Discussion of the mechanistic aspects for galantamine would also apply in this case. A report on autism indicated that the drug could improve speech [22]. Additionally, a recent review provides evidence for involvement of the ROS – OS –AO mechanism in autism [23].

### f.   Piperine

Piperine (Figure 6), an alkaloid spice responsible for the pungency of pepper and a catechol diether, has been investigated in Alzheimer's disease therapy. Also the drug enhances cognitive functions as well as the standard drug donepezil [24]. A dual mechanism appears to apply namely AO activity and esterase inhibition. Additional modes of action are anti-apoptosis and anti-inflammation. Another study showed results superior to donepezil [25] in which OS was reduced. Numerous medicinal plants possess profound central nervous system (CNS) effects and AO activity [26]. Possible modes of action involve decreases in lipid peroxidation and esterase enzymes. A 2015 study revealed enhanced cognitive function; also, anti-inflammatory and anti-apoptotic effects were noted [27]. Again, like with the previously mentioned drugs, the ester undergoes catalysis resulting in the generation of an AO phenol. This is a part of a planned series on brain diseases based on the unifying theme of ROS – OS –AO, which has been applied previously to many

bioactive compounds and drugs. Also, a treatment of structure-activity relationship (SAR) for drugs relating to the various brain diseases discussed in this series of commentaries is forthcoming.

## Acknowledgement

## References

1. Barry Halliwell, John MC Gutteridge (1999) Free Radicals in Biology and Medicine. Oxford University Press, 3rd Edn, Oxford, UK.

2. Kovacic P, Somanathan R (2014) Novel Mechanism for Advanced Glycation End Product (AGE) Toxicity: α-Dicarbonyls, Electron Transfer, Radicals, Oxidative Stress, and Antioxidants. In: Systems Biology of Free Radicals and Antioxidants. Springer-Verlag Berlin Heidelberg, Germany: 3405-3418.

3. Kovacic P, Somanathan R (2014) Inflammation and Anti-Inflammatory Agents- Reactive Oxygen Species and Toxicity. In: Systems Biology of Free Radicals and Antioxidants. Systems Biology of Free Radicals and Antioxidants pp. 3197-3216.

4. Ferreira ME, De Vasconcelos AS, Da Costa Vilhena T, Da Silva TL, Da Silva Barbosa A, et al. (2015) Oxidative stress in Alzheimer's disease: Should we keep trying antioxidant therapies? Cellular and Molecular Neurobiologies 35(5): 595-614.

5. Kryscio RJ, Abner EL, Caban Holt A, Lovell M, Goodman P, et al. (2017) Association of Antioxidant Supplement Use and Dementia in the Prevention of Alzheimer's Disease by Vitamin E and Selenium Trial (PREADViSE). JAMA Neurology 74(5): 567-573.

6. Raszewski G, Chwedorowicz R, Chwedorowicz A, Gustaw Rothenberg K (2016) Homocysteine, antioxidant vitamins and lipids as biomarkers of neurodegeneration in Alzheimer's disease versus non-Alzheimer's dementia. Annals of Agricultural and Environmental Medicine 23(1): 193-196.

7. Duvoix A, Blasius R, Delhalle S, Schnekenburger M, Morceau F (2005) Chemopreventive and therapeutic effects of curcumin. Cancer Letters 223(2): 181-190.

8. Shrikant Mishra, Kalpana Palanivelu (2008) The effect of curcumin (turmeric) on Alzheimer's disease: An overview. Annals of Indian Academy of Neurology 11(1): 13-19.

9. Hamaguchi T, Ono K, Yamada M (2010) Review: Curcumin and Alzheimer's disease.CNS Neuroscience and Therapeutics 16(5): 285-297.

10. John M Ringman, Sally A Frautschy, Gregory M Cole, Donna L Masterman, Jeffrey L Cummings (2005) A Potential role of the curry spice curcumin in Alzheimer's disease. Curr Alzheimer Res 2(2): 131-136.

11. Kim JY, Choi DS, Jung MY (2003) Antiphoto-oxidative activity of sesamol in methylene blue- and chlorophyll-sensitized photo-oxidation of Oil. Journal of Agricultural and Food Chemistry 51(11): 3460-3465.

12. T Ohsawa (1991) Sesamol and sesaminol as antioxidants. New Food Industry 33(6): 1-5.

13. Wynn JP, Kendrick A, Ratledge C (1997) Sesamol as an inhibitor of growth and lipid metabolism in Mucor circinelloides via its action on malic enzyme. Lipids 32(6): 605-610.

14. Ansari MA, Fatima Z, Saif Hameed (2014) Sesamol: A natural phenolic compound with promising anticandidal potential. Journal of Pathogens 2014(2014): 12 pages.

15. Liu Z, Chen Y, Qiao Q, Sun Y, Liu Q, et al (2017) Sesamol supplementation prevents systemic inflammation-induced memory impairment and amyloidogenesis via inhibition of nuclear factor kappaB. Molecular Nutrition and Food Research 61(5).

16. Winblad B, Grossberg G, Frolich L, Farlow M, Zechner S, et al. (2007) IDEAL: A 6-month, double blind, placebo-controlled study of the first skin patch for Alzheimer disease. Neurology 69(4): S14-22.

17. P Camps, D Muñoz Torrero (2002) Cholinergic drugs in pharmacotherapy of Alzheimer's disease. Mini Reviews in Medicinal Chemistry 2(1):11-25.

18. Michael Heinrich (2004) Snowdrops: The heralds of spring and a modern drug for Alzheimer's disease. Pharmaceutical Journal 273(7330): 905-906.

19. Mashkovsky MD, Kruglikova Lvova RP (1951) On the pharmacology of the new alkaloid galantamine. Farmakologia Toxicologia (Moscow) 14: 27-30.

20. Kovacic P, Osuna JA (2000) Mechanisms of anticancer agents: Focus on oxidative stress and electron transfer. Current Pharmacutical Design 6(3): 277-309.

21. Birks J, Harvey RJ (2006) Donepezil for dementia due to Alzheimer's disease. Cochrane Database of Systematic Reviews 25(1): CD001190.

22. Chez Michael G, Buchanan Thomas M, Becker Marina, Kessler Jami, Aimonovitch Mary C, et al. (2003) Donepezil hydrochloride: a double-blind study in autistic children. Journal of Pediatric Neurology 1(2): 83-88.

23. Peter Kovacic, Ratnasamy Somanathan (2017) Mechanistic aspects of autism involving electron transfer, reactive oxygen species, oxidative stress, pollutants, antioxidants, cell signaling and genes. Novel Approaches in Drug Designing and Development 1(3): 8 pages.

24. Elnaggar YS, Etman SM, Abdelmonsif DA, Abdallah OY (2015) Intranasal piperine-loaded chitosan nanoparticles as brain-targeted therapy in Alzheimer's disease: Optimization, biological efficacy, and potential toxicity. Journal of Pharmaceutical Sciences 104(10): 3544-3556.

25. Yusuf M, Khan M, Khan RA, Ahmed B (2012) Preparation, characterization, in vivo and biochemical evaluation of brain targeted piperine solid lipid nanoparticles in an experimentally induced Alzheimer's disease model. Journal of Drug Targeting 21(3): 300-311.

26. Chonpathompikunlert P, Wattanathorn J, Muchimapura S (2010) Piperine, the main alkaloid of Thai black pepper, protects against neurodegeneration and cognitive impairment in animal model of cognitive deficit like condition of Alzheimer's disease. Food and Chemical Toxicology 48(3): 798-802.

27. Elnaggar YS, Etman SM, Abdelmonsif DA, Abdallah OY (2015) Novel piperine-loaded tween-integrated monoolein cubosomes as brain-targeted oral nanomedicine in Alzheimer's disease: pharmaceutical, biological, and toxicological studies. International Journal of Nanomedicine 10: 5459-5473.

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