

Phytochemicals, Antioxidants, and Cholinesterase Inhibitory Profiles of *Elatostema Papillosum* Leaves: An Alternative Approach for Management of Alzheimer's Disease

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Article Info

Article Notes

Received: August 1, 2018
Accepted: October 8, 2018

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Keywords:

Alzheimer's disease
Antioxidant
Phytochemicals and Oxidative stress

ABSTRACT

Alzheimer's disease (AD) is a devastating neurodegenerative disorder of the brain characterized by memory loss and, impaired judgment and language use. As AD incidence increases with age, AD has become a large socioeconomic burden that will only continue growing as populations age. Natural compounds that possess polyphenolic (phenolics and flavonoids) content and antioxidant property have the capacity to reduce the progression and symptoms of neurodegenerative diseases, including AD. In this mini-review, we emphasize the pathomechanisms of AD, including oxidative stress and modulatory roles of natural antioxidants in preventing AD. We discuss the antioxidant, phytochemical, and anticholinesterase properties of the plant *Elatostema papillosum*, which are relevant to the management of AD.

Introduction

Alzheimer's disease (AD) is a neurodegenerative disorder of the brain characterized by memory dysfunction, impairment in language and judgment capacity. AD is the most common cause of presenile and senile dementia worldwide¹. In 2006, 26.6 million AD patients were diagnosed; this is expected to rise to 106.8 million by 2050². The prevalence rate of AD doubles every five to ten years and this incidence increases exponentially with age, rising from 3 % among those 65-74, to almost 50 % among those 85 or older³. Thus, dementia and AD have become primary areas of research due to their enormous social, economic, and health care impacts. Indeed, after cancer and coronary heart disease, AD is the third most expensive disorder in the United States; moreover, total worldwide societal costs were estimated to be \$ 315 million in 2005, with about 70 % of costs occurring in developed countries⁴.

The etiology of AD is not yet completely understood. However, both genetic and environmental factors are responsible for late-onset and sporadic AD⁵, with aging being the greatest risk factor for AD⁶. The apolipoprotein E (ApoE) genotype is the second greatest risk factor for AD after age. ApoE has three isoforms ApoE2, ApoE3, and ApoE4. Among the isoforms, ApoE4 is the most common and least protective variant of AD^{7,8}. Two other important factors linked to AD are the overproduction of A β protein and abnormal tau protein. Kuszczuk et al., (2009) and Scheff et al., (2007) reported that the highly-phosphorylated tau protein and overproduction of A β protein initiate the loss of neurons, neuropil, and synaptic elements^{9,10}, which leads to cognitive function deficiencies and dementia. It is believed that accumulation of extracellular A β protein plays a central role in the pathogenesis of AD. The mechanism of

A β formation is complex, but several studies suggest that enhanced oxidative stress provoked by A β is associated with AD¹¹.

Oxidative stress and Alzheimer's disease

Antioxidants are molecules involved in scavenging reactive species, which can be caused by oxidative stress (OS). Antioxidants have a wide range of effects in various disease conditions and can help to prevent onset and progression of certain diseases. OS is emerging as a key mechanism underlying the pathogenesis of AD in both human brains and animal models, alongside excess deposition of A β protein, neurofibrillary tangle (NFT) formation, and metabolic dysfunction¹²⁻¹⁴. The relationship between systemic OS and AD has received increased recognition in the last decade⁸. In addition, accumulation of intracellular free radicals dysfunctions the activities or expressions of antioxidant enzymes superoxide dismutase (SOD) and catalase, have also been described in the brain of a patient diagnosed with AD¹⁵. Moreover, oxidative damage can occur in peripheral cells as well as neuronal cells when oxidative homeostasis is disturbed; the resultant excessive production of reactive oxygen damages the cellular antioxidant defense mechanisms and triggers the occurrence of AD⁸.

There are a number of sources of OS in AD patients, including increased levels of iron-redox-active state in NFT as well as in A β protein¹⁶, activated microglia surrounded by the most senile plaques, which produce NO and O₂⁻¹⁷. Amyloid- β protein precursor (A β PP) responsible for formation of reactive oxygen¹⁸, abnormalities in the mitochondrial genome⁸, and deficiencies in key metabolic enzymes¹⁹. Reactive oxygen species (ROS) are those that include reactive oxygen ions and peroxides and cause detrimental effects at high concentration to all biomolecules (DNA, RNA, proteins and lipids), leading to pathological conditions in humans¹⁸. The imbalance between cellular production of ROS and the inability of cells to defend against ROS causes OS, which contributes to age-related neurodegeneration and cognitive decline⁸.

Antioxidants as a Therapeutic Target in Alzheimer's Disease

Antioxidants play a functional role in the pathogenesis of the different diseases, including AD. Therefore, diverse antioxidants N-acetylcysteine, curcumin, resveratrol, vitamin E, vitamin C, ferulic acid, coenzyme Q (CoQ), selenium, and melatonin, have been tested for their protective role in cognitive performance in both healthy individuals, as well as those with mild cognitive impairment and AD²⁰. However, despite promising effects of these compounds on cellular oxidative status *in vitro* and *in vivo*, the realistic evidence of their therapeutic potential in humans is limited. Recently, Mazzanti et al., reviewed a

number of published and ongoing clinical trials with the use of curcumin and resveratrol for AD therapy²¹. Moreover, Morris et al., (2002) and Engelhart et al., (2002) reported that eating foods rich in antioxidants such as beta carotene and vitamins C and E are associated with lower risk of AD and dementia^{22,23}. Furthermore, under normal conditions, OS and cellular damage are combated by endogenous antioxidant compounds and enzymes. However, the brain is highly vulnerable to oxidative damage due to high levels of ROS and poor antioxidant systems.

In addition, ROS-mediated mitochondrial damage plays a key role in AD pathogenesis. Therefore, agents that target mitochondrial dysfunctions and reverse oxidative stress may serve as novel AD therapeutics. One such therapeutic might be MitoVitE, also known as mitotocopherol, which protects mitochondria from oxidative stress via inhibition of lipid peroxidation⁸. Pocernich et al., (2011) reported that in both AD and mild cognitive deficit brains with significantly decreased levels of antioxidant enzymes, the brains became vulnerable to deposition of A β protein²⁴. Consequently, it was suggested that one way of enhancing brain defense was by improving the antioxidant defense system, particularly endogenous glutathione (GSH), glutathione-related enzymes, catalase, and superoxide dismutase.

Elatostema papillosum and Alzheimer's Disease Treatment

Agents which elevate acetylcholine (ACh) levels are essential targets for AD treatment. ACh is an organic neurotransmitter found in the synapses of the cerebral cortex. Decreased levels of ACh and insufficient cholinergic function have been correlated with cognitive deficits seen in AD patients²⁵. Therefore, several strategies have been established to increase ACh levels, such as using the ACh precursor (choline)²⁶, muscarinic and nicotinic agonists²⁷, ACh releasers²⁸, and acetylcholinesterase (AChE) inhibitors²⁹. Among these, the acceptable option for AD treatment is restoration of ACh levels through inhibition of two major forms of cholinesterase enzymes, AChE and butrylcholinesterase (BChE)²⁹. To date, only three cholinesterase inhibitors, donepezil, galantamine and rivastigmine have been approved by the US Food and Drug administration to treat AD³⁰. However, these compounds have been reported to have therapeutic activity along with adverse side effects, such as hepatotoxicity, short duration of biological action, low bioavailability, and gastrointestinal disturbances³¹. Therefore, natural sources, especially plants have been gaining attention for putative use as novel cholinesterase inhibitors and/or antioxidants.

Elatostema papillosum (*E. papillosum*), a member of Urticaceae family, is a suberect herb (commonly known as Elya) available in Australia and Oceania, China, Bhutan, India, and Bangladesh. From existing ethnobotanical

literature, it is clear that *E. papillosum* has marked folkloric reputation as useful in combatting different afflictions, such as hysteria and abdominal pain³². Interestingly, some characteristics of hysteria overlap with symptoms of AD³³. Recently, many research groups have reported that antioxidant-enriched plants and plant metabolites possess remarkable cholinesterase inhibition capacity^{12,13,34}. Our group also reported that *E. papillosum* showed marked cholinesterase inhibition and free radical (DPPH and hydroxyl radical) scavenging activities. Furthermore, the plant possessed potent phenolic and flavonoid content along with a positive correlation between antioxidant and cholinesterase inhibition potential¹⁴. Recent evidence suggests that the secondary metabolites, flavonoids, have positive effects against dementia and AD³⁵⁻³⁷. Our results were consistent with those of the data published previously^{12,13,34} and suggest that *E. papillosum* may be a valuable method for treating AD by targeting both the OS and impaired cholinergic signaling characteristic of AD.

Conclusions

Medicinal plants having potential antioxidant and free radical scavenging capacity can be applied to reduce dementia and to treat AD. Polyphenolic compounds are the most abundant antioxidants in the plant kingdom harboring neuroprotective effects. As, *E. papillosum* is a significant source of phenolics and flavonoids, which act as natural cholinesterase inhibitors and free radical scavengers, this plant may be a powerful future medicine for treating and managing AD.

Acknowledgement

The authors are grateful to the Department of Pharmacy, International Islamic University Chittagong, Bangladesh for providing necessary facilities for this research work. The authors also thank Mr. John Vaughen, a native English speaker, for his critical comments and language correction.

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