A MINI REVIEW OF NATURAL ANTIOXIDANT FOR ALZHEIMER'S DISEASE

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ABSTRACT

Alzheimer's disease (AD) is the leading cause of dementia, an estimated 5 million people in the US suffer at a cost of more than $70 billion per year. The main theories on the causes of AD include amyloid-beta (Aβ), tauopathy, inflammation and oxidative stress. The purpose of writing this review article is to look at the various types of natural antioxidants and the mechanism of action of each against AD therapy. **Method**: this article reviews antioxidants to activity of action againts AD. The following databases were searched from their inception: Google scholar, Science direct, PubMed. The document relevant analyzed and included in the review. Therefore, this paper mainly focuses on the recent developments of common used antioxidant therapies for AD. **Results**: Alzheimer's disease correlates with free radicals which can be minimized by consuming natural antioxidants from foods such as vitamins C and E, carotenoids (β-carotene and astaxanthin), Flavonoids, Green tea, Huperzine, Ginko biloba, Centella asiatica, Curcumin, Melissa officinalis, Polygala tenuifolia, Salvia miltiorrhiza bung and Withaniasomnifera (L), with a variety of different mechanisms of action for each of these types of natural antioxidants. **Conclusion**: The therapeutic potential of AD in natural antioxidants plays an important role in prevention and treatment

Key Words: Natural antioxidant, Alzheimers disease, Mechanism of action, Prevention and Treatment

INTRODUCTION

Alzheimer's disease is a degenerative brain disease and the most common cause of dementia[1]. The number of the disease is projected to reach 106.8 million worldwide by the year 2050, therefore, the disease is a growing public health concern with major socioeconomic burden[2]. The risk of AD varies from 12% to 19% for women over the age of 65 years and 6% to 10% for men[3] and rises exponentially with age, such that up to 47% of individuals over the age of 80 develop AD[4]. Dementia is a syndrome, a group of symptoms that has a number of causes. The characteristic symptoms of dementia are difficulties with memory, language, problem-solving and other cognitive skills that affect a person's ability to perform everyday activities. These difficulties occur because nerve cells (neurons) in parts of the brain involved in cognitive function have been damaged or destroyed.

METHODS

A comprehensive literature search was performed from the inception of the study on these online databases: Google scholar, Science direct and PubMed. The search terms that were used were "natural antioxidant", and "Alzheimer's Disease". The search was limited to English articles only.

RESULTS AND DISCUSSION

Alzheimer's disease is highly correlated with free radicals and cellular redox imbalance[5] . Have become the culprit for influencing human health. In order to scavenge superfluous free radicals and maintain the balance of homeostasis in human body as well as accomplish the prevention and treatment of diseases, the consumption of antioxidants is necessary. However, synthetic antioxidants have toxic effects to some extents. Therefore, the uptake of natural antioxidants from foods is the first choice because natural antioxidants not only play an important role in the prevention and adjunctive treatment of diseases but also can avoid the adverse reactions to human health. In this article, common natural antioxidants such as vitamins (vitamin C and E), carotenoids (β-carotene and astaxanthin), flavonoids and some traditional herbal antioxidants also exhibit potential for AD therapy in foods are summarized. In the antioxidant Systems, Endogenous defense mechanisms, including enzymatic antioxidant systems and cellular molecules, protect against free radical-induced cellular damage. SOD, catalase, and glutathione peroxidase are three primary enzymes involved in direct elimination of active oxygen species (superoxide radical and H_2O_2). A number of dietary factors such as antioxidants, vitamins, polyphenols, and fish have been reported to decrease the risk of AD[6]. A summary of the natural antioxidant used to treat AD is presented in table 1, from this table are enumerated of describing natural antioxidants, foods rich in natural antioxidants and references

Table 1. The natural antioxidants in prevention and treatment of Alzheimer's disease.

Natural antioxidants	Foods rich in natural antioxidants	Reference
Vitamin E (α-tocopherol	Corn oil, Soybean oil, Margarine, and Dressings	7
vitamin C	Citrus fruits, Broccoli, Russels sprouts, Raw bell peppers, and Strawberries	8
β-carotene	Spinach,Kale,Cantaloupe, Mangoes, Pumpkin,Papayas, Carrots and Sweet potatoes	9
Astaxanthin	Shrimp shell, Oysters and Salmons	10
Green tea	Green tea	11
Flavonoids	Plants, Berries, Honey Chinese herbs	12
Huperzine A	Extract of Huperzia serrata	13
Gingko biloba	The Ginkgo tree extract EGb 761	14
Curcumin	Curcumin root	15
Centellaasiatica	Centellaasiatica leaf	16
Melissa officinalis (Labiatae)	Melissa officinalis leaf	17
Polygala tenuifolia (Polygalaceae)	Polygala tenuifolia (Polygalaceae) root	18
Salvia miltiorrhiza bung	Salvia miltiorrhiza bung root	19
Withaniasomnifera (L.) Dun	Withania somnifera (Solanaceae) root	20

In the aging model mice induced by *D*-galactose, astaxanthin treatment can recover the activities of GSH-Px and SOD, enhance GSH content and reduce oxidative stress, improve pathological injury of hippocampus, and increase the expression level of BNDF, thus achieving the anti-aging role finally[10]. Green tea polyphenols have obvious protective effect on neurodegenerative diseases such as Alzheimer's disease. In the pathogenesis of AD, amyloid beta (Aβ) aggregation can lead to the generation of a large amount of free radicals such as active oxygen species and active nitrogen species, correspondingly resulting in oxidative stress and accelerating neuronal death. (−)-Epigallocatechin-3-gallate (EGCG) as the effective component in green tea polyphenols was reported to significantly reduce the Aβ deposition in transgenic mice with the over-expression of Aβ and increase the activity of α-secretase, suggesting that green tea polyphenols have an important role in decreasing oxidative stress in the

brain of AD patients[21]. Another study on model mice with high-fat and high-sugar diet for 4 weeks and green tea polyphenol solution instead of drinking water revealed that green tea polyphenols can result in the significant reduction in the permeability of large artery and ROS levels as well as protein expression level of NAD(P)H oxidase subunit $p22^{phox}$ and $p67^{phox}$ in high-fat and high-sugar diet-induced model mice. As NAD(P)H oxidase is an important source of ROS *in vivo*, the antioxidant effect of green tea polyphenols *in vivo* may implement through inhibiting the expression of NAD(P)H oxidase[22]. The contents of derivatives from ROS metabolites in patients with hepatocellular carcinoma reveal a significant decrease when provided with green tea tablets during the chemotherapy treatment[23]. In addition, the free radical analysis system 4 (FRAS4) has shown that the potential of biological antioxidant is greatly improved. Moreover, green tea polyphenols also have an important function in inhibiting tumor and inflammation[24,25,26] . The flavonoids extracted from some plants have an excellent antioxidant function for the protection of vascular system and the treatment of arthritis and Alzheimer's disease. In arthritis model mice treated through oral administration of *Daphne genkwa* flavonoids extract at the dose of 50 mg/kg for 15 consecutive days, the arthritis score (ACS) was decreased while the expression of SOD and GSH-Px enzymes was increased when compared with the control group[27,28]. A study on 32 elderly people treated with fresh *G. biloba* extract revealed the improved microcirculation of skin and liver, accelerated scavenging of free radicals and the improvement of arteriosclerosis. 30 days after 270 mg *G. biloba* extract or placebo treatment, the red cell perfusion nodes and blood flow of small veins, and red blood cell volume revealed an obvious higher in the *G. biloba* extract treatment group when compared with the control group. Moreover, a significantly higher level of GSH as a radical scavenger in the *G. biloba* extract treatment group than that of the control group was also observed. Therefore, *G. biloba* has a beneficial effect on the health of the elderly population[29]. Flavonoids from *Panaxnotoginseng* have strong antioxidant activity[30]. *Salvia miltiorrhiza* also contains a lot of bioactive components with antioxidant and anti-inflammatory functions. Guo et al reported that tanshinol plays a protective role in apoptosis induced by γ-ray through reducing the generation of ROS, inhibiting the release of cytochrome C and blocking the activation of apoptotic factors[31] . The pretreatment of tanshinol on L-02 cells can significantly reduce the level of ROS caused by γ-ray and the activity of Caspase 3 as well as the expression of Bax. Tanshinone IIA can weaken neuronal damage induced by hydrogen peroxide[32]. Flavonoids in *Glycyrrhiza* such as licorice chalcone and licorice isoflavones also have strong antioxidant activity, which plays an important role in the clearance of free radicals and prevention of diseases[12,33]. Another prescription "Suhexiang pill" can reduce Aβ deposition in model mice with Alzheimer's disease, enhance memory and inhibit the apoptosis caused by Aβ and decrease oxidative stress in brain[34]. A natural antioxidant mechanism of action of AD reviewed are presented in Table 2

Tabel 2. Natural antioxidant mechanism of action of AD

Natural antioxidant	Mechanism of action /target	Reference
Vitamin E (α-tocopherol	Suppresses brain lipid peroxidation and significantly reduces Aβ levels and senile plaque deposition	35
Vitamin C	Decrease high levels of isoprostanes and oxidative stress in vivo, enhance NO bioavailability, restore the regulation of shear stress in arterioles, and normalize systemic blood pressure	36
β-carotene	Synergistically interact against lipid peroxidation	37
Astaxanthin	The involvement of extracellular signal-regulated kinases 1 and 2 (ERK1/2) signaling and the downstream activation of HO-1 on observed neuroprotection from the amyloid beta peptides. AXT ultimately reduced apoptotic-related mediators caspase 3 and Bax	38
Green tea	EGCG The principal bioactive component found in green tea, has anti-inflammatory properties by modulating different molecular pathways. Regarding AD's syndrome, EGCG mainly induces reduction in Aβ accumulation, by modulating several biological mechanisms.	39
Flavonoids	Their specific interactions within the ERK and PI3-kinase/Akt signaling pathways, at the level of receptors or kinases, have been shown to increase the expression of neuroprotective and neuromodulatory proteins and increase the number of, and strength of, connections between neurons.	40
Huperzine A	Reduce glutamate-induced toxicity in neurons, possibly through modulation of glutamate-NMDA receptor interaction, or of the passage of Ca2+ through associated ion channels	13

Gingko biloba	Block Abeta1-42-induced Ca^{2+}dyshomeostasis mediated by formation of toxic mediators such as H_2O_2 and PAF	41
Curcumin	Corrected Abeta-induced caspase-3 activation, Bcl-2 downregulation and Akt phosphorylation	42
Centella asiatica	Protect cortical neurons from glutamate-induced excitotoxicity in vitro	43
Melissa officinalis (Labiatae)	Inhibitor of AChE and binding to muscarinic and nicotinic receptors	44
Polygala tenuifolia (Polygalaceae)	Upregulated choline acetyltransferase (ChAT) activity and increased nerve growth factor (NGF) secretion	44
Salvia miltiorrhiza bung	Inhibit neuronal cell death by inhibition of presynaptic glutamate release, and nitric oxide (NO) formation.	19
Withaniasomnifera (L.) Dun	Reversed the reduction in cholinergic markers (e.g. ACh, ChAT). Enhances liver LRP (low density lipoprotein receptor- related protein) and decreases β-Amyloid formation by Aβ- degrading protease neprilysin (NEP) in brain	45

CONCLUSION

Antioxidants play an important role in counteracting free radicals and maintaining the balance of the body. In modern life, the application of synthetic drugs for health care and disease prevention does not seem the optimal choice. The contribution of natural antioxidants plays an important role in the prevention and treatment of AD, and can meet the demands of modern society. The process of extracting and preserving natural antioxidants is a development target for the food and health care industry in the future. The following natural antioxidants have different mechanisms of action such as vitamin E and carotenoids (β-carotene) which can suppress lipid peroxidation and reduce Aβ levels, Vitamin C reduces isoprostane levels and oxidative stress, Astaxanthin works to suppress the apoptotic mediators caspase 3 and Bax, Flavonoids as neuroprotective, neuromodulator and synaptogenesis, Green tea has the main bioactive component EGCG as an anti-inflammatory and induces a reduction in Aβ accumulation, Huperzine A modulates glutamate-NMDA receptor interactions, Ginko biloba works to block Abeta1 -42, Centella asiatica works to protect cortical neurons from glutamate-induced excitotoxicity, Curcumin activates corrected Abeta-induced caspase-3 and downregulates Bcl-2 and Akt phosphorylation, Melissa officinalis inhibits AChE and binds to muscarinic and nicotinic receptors, Polygala tenuifolia activates secretion nerve growth factor (NGF), Salvia miltiorrhiza bung works to inhibit neuronal cell apoptosis by inhibiting presynaptic glutamate release and nitric oxide (NO) formation, Withaniasomnifera (L) works to reduce Aβ formation by the neprilysin protease (NEP). Each of these natural antioxidants has a different mechanism of action in endogenous defense, including enzymatic antioxidant systems and cellular molecules, protecting against cellular damage caused by free radicals.

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