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REVIEW ARTICLE

The Effect of Phytoestrogens on Cognitive Function and Alzheimer's Disease

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ABSTRACT

Dementia is a neurodegenerative disorder that leads to a significant cognitive loss. It was shown that the rise in life expectancy and the number of elderly people in the community led to an increasing trend in incidence and prevalence of Alzheimer's disease. Several studies reported that nutritional factors can affect the development and rate of the disease. Food strategies and lifestyle may be effective in prevention of Alzheimer's development. Phytoestrogens are non-estradiol compounds with a diphenolic and heterocyclic structure. Phytoestrogens have potential to bind to estrogen receptors and exhibit biological properties of estrogen. They are estrogen receptor modulators, acting as estrogen agonists or antagonists. Through binding to estrogen receptors, phytoestrogens may increase survival, growth, and plasticity of brain cells. One of the most important effects of phytoestrogens is improvement of visual-spatial memory. Acting as estrogen, phytoestrogens promote the cognition and memory through improvement of endothelium vasodilatation and increase supplying blood to brain cells. In addition, phytoestrogens possess antioxidant capacity which may prevent neurodegenerative diseases when passing through the blood-brain barrier. The use of phytoestrogens and their dietary sources such as soybeans can be beneficial in prevention of Alzheimer's disease.

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Introduction

Recognition is a process in which a person acquires and uses the received information (1). Recognition occurs through a series of interdependent mental processes and helps the person to adapt to environmental factors. It includes basic (attention, memory, perception) and advanced (knowledge and executive functions) cognitive skills (2). Saving information in the memory have three stages. First, the information taken from the surrounding environment is transferred into sensory-perceptual memory (3).

Then, the information is encrypted in the short-term working memory and finally the information is stored in the long-term memory to be evaluated later.

Dementia is a neurodegenerative disorder characterized by a significant loss in cognitive function (3). The prevalence of dementia increases with age. The most common form of dementia is Alzheimer's disease, which consists about 60-70% of the cases (4). The disease is consisted of three stages of mild (1-2 years), middle (2-5 years), and severe (over 5 years). Gradually, with the advancement of

the illness, the individual loses the ability to do his or her daily routine activities and ultimately may not be capable to have an independent life (5). The world population has a rapid aging trend, especially in low or middle income societies, and this is associated with a surge in the prevalence of dementia (5). After the age of 60, with an increase of 5.9 years in age, the prevalence of dementia is doubled (4) and every 4.1 seconds, a new case is added to the world population with dementia. Thus, preventive approaches are more important than treatment efforts (4).

Statistics and Costs of Alzheimer's Disease

In 2010, a total of 35.6 million people were suffering from dementia. These statistics are doubling every 20 years. It is estimated that in 2030, 65.7 million people and by 2050, 115.4 million people will be affected by the disease (5). The consequences of the illness are devastating for the patients, their relatives, and also the community. In 2010, 604 billion US\$ was spent for the patients care. However, because most of the care is provided by the patients' family who do not receive any payment, the estimated medical costs only cover 16% of the total costs (5).

The Effect of Gender on the Risk of Alzheimer's Disease

Menopause is a part of aging process in women which results in a drastic decrease in concentrations of estrogen and progesterone. The lack of estrogen for long-term can reduce estrogen receptors in the brain. Reduced estrogen receptors in the brain is shown to be associated with a decline in cognition, behavioral changes, and impairment in the memory (6). Unlike women, sex hormones in men decrease gradually and thus the behavioral changes are seen less severe. Accordingly, the prevalence of dementia in women over 65 was found to be 14-32% higher than men (7). Although hormone-replacement therapy has neuroprotective effects, long-term use of the hormones increases the risk of hormone-related cancers, stroke, and thrombosis (7, 8). Nonetheless, phytoestrogens including soy isoflavones can use as natural substitutes for factory-made hormones without causing side-effects relative to hormone-replacement therapy (3, 9).

The Effect of Nutrition on Alzheimer's Disease

Several studies have shown that nutritional factors such as those involved in oxidative stress can promote neural cell membrane damage (10). Similarly, food strategies and lifestyle can be effective in prevention of Alzheimer's disease development. However, due to complexity of the disease, more studies are needed to

identify all nutritional factors relative to progression and prevention of the disease. A better understanding of the mechanisms by which nutritional factors such as phytoestrogens affect the process of Alzheimer's disease will help for designing better interventions for treatment of the disease (11).

Phytoestrogens

Phytoestrogens are non-estradiol compounds with a di-phenolic and heterocyclic structure (11, 12). Thanks to their structure, they have ability to bind to estrogen receptors and develop physiological and psychosomatic properties of estrogen (11). Phytoestrogen are classified in four main groups: isoflavones (found in soy products and red clover), lignans (available in flaxseed), coumestans (in clover and alfalfa), and stilbens (in grape skin, berries, peanut, etc.) (7, 3, 13). Among phytoestrogens, isoflavones have been studied more (3).

Isoflavones are flavonoids, a large group of phytochemicals with numerous biological properties in prevention of diseases (14). In foods, isoflavones are in the form of inactive glucosides, but in the intestine they are broken into the active compounds, i.e. aglycons, by glucosidase enzymes of bacteria, (3, 12). The strongest aglycons are genistein and daidzein although their effect is weaker than estrogen (6). For instance, the tendency of genistein for binding to estrogen receptor is 50-100 times more than daidzein (6).

Mechanism of Phytoestrogen Action in Alzheimer's Prevention

Phytoestrogens exert their effects through binding to and modulating estrogen receptors, acting as either an agonist or antagonist of estrogen (3, 5). Estrogen receptor is present in both genders, but in females it is more expressed and transcribed than males (15). There is two types of estrogen receptor in the brain: estrogen receptor-alpha and estrogen receptor-beta. The quantity of these receptors are equal in the hippocampus but in the forehead cortex, the alpha receptor is less than beta (5). It is shown that isoflavone tendency for estrogen receptor-beta is 7-30 times higher than estrogen receptor-alpha (16, 17).

The effect of isoflavones, as estrogen mimetic, on the brain is not well known, but a number of mechanisms may explain the beneficial effects of phytoestrogens on cognitive function. The sexually dimorphic nucleus of the preoptic area (SDN-POA) is located in the hypothalamus and is usually 2-2.5 times larger in females than males. The exposure of gonadectomized rats to genistein increased the size of SDN-POA, indicating that phytoestrogens

may alter brain morphology (11). The phytoestrogens via estrogen receptor-beta can increase the survival, growth, and plasticity of brain cells. Soybean isoflavones can activate estrogen receptor-beta in the hippocampus and the forehead cortex, and thus have a significant effect on memory, mental flexibility, and functional performance (3).

Estrogen receptor-beta plays an important role in development of brain tissue, neuroplasticity, learning and the hippocampal memory and has a wide interference with the estrogenic activity of the brain that plays a role in neural survival, and mitochondrial function and destruction. The activation of estrogen receptor-beta leads to reduced risk of progression of related cancers (4). One of the most important effects of phytoestrogens is its effect on visual-spatial memory. Visual spatial memory is responsible for displaying, translating, constructing and reminding of symbolism information. It is shown that administration of estrogen to wild type rats caused memory loss, but improved memory in ovariectomized rats (11). Evidence from randomized clinical trials showed that supplements with phytoestrogens can be useful for executive performance, mental flexibility, maintaining concentration, verbal memory, visual-spatial memory, mental health, speech health, and processing speed (3).

On the other hand, a case-control study indicated that a diet rich in phytoestrogens in men reduced the level of calbindin and increased cyclo-oxygenase-2 (11). Cyclo-oxygenase-2 is a common inflammatory factor in Alzheimer's disease and calbindin is a calcium-binding protein that plays a protective role against apoptosis. Phytoestrogens may exert beneficial effects on brain independently through affecting other tissues (7). For instance, following the effect of phytoestrogens on the endothelium, the vessels become dilated and the blood supply to the brain increases, which results in improvement in cognition and memory. Phytoestrogens bind to estrogen receptor in the nucleus and the endothelium membrane, and stimulate the transcription of the genes producing endothelium nitric oxide synthase. With an increase in nitric oxide, the perfusion of the brain also increases (7).

Genistein, as one of the phytoestrogens, has antioxidant effects against ultraviolet light and chemicals. It can cross the blood-brain barrier and exhibit its antioxidant effect against neurodegenerative diseases (18). Genistein protects nerve cells and increases the regulation of neurotrophic secretion of the brain. Animal models have shown that genistein reduces neuronal decline and improves cell death induced by amyloids (3). Genistein can also protect the cells

against toxicity induced by hydrogen peroxide (18). Phytoestrogens also increase the activity of antioxidant enzymes such as catalase, superoxide dismutase, glutathione peroxidase, and glutathione reductase, and can have a protective effect against oxidative stress and accumulation of oxidative damage (15).

Soybean isoflavones were shown to affect the cholinergic system of the brain and reduce the age-related neurological loss and cognitive decline in male rats (18). Supplementation with soybean can prevent memory loss by preventing cholinergic transmission and reducing free radical production (3). Cognitive effects of phytoestrogens in female rats may also be due to increased presence of acetylcholine transferase mRNA located in the forehead cortex which was associated with brain protection and function (18).

Brain-derived neurotrophic factor (BDNF) is a neurotrophic factor extracted from the brain. BDNF plays a critical role in survival and differentiation of a number of neurons (19). BDNF increases the survival of the hippocampal neurons, preserves neurogenesis of the hippocampus, and is involved in learning and memory operation. Phytoestrogens and estradiols have shown to increase BDNF *in vitro*. Animal studies on rats showed an increased spatial learning and memory in ovariectomized rats supplemented with phytoestrogens and estradiols (19). The displayed effect was similar for phytoestrogens and estradiols but unlike estradiols, phytoestrogens do not have an effect on reproductive system, so they improve cognitive function without increasing the risk of hormone-dependent cancers (4, 19).

A formulation containing genistein, daidzein, and equol, is an excellent combination that can be effective in improving neuronal survival and brain defensive enzymes such as hemostasis-amyloid enzyme, and enzymes for the progression of cerebrovascular mitochondrial function (3, 4). In addition, the formulation does not affect reproductive system not it increases the risk of hormone-dependent cancers. Long-term exposure to this combination can prevent or reduce symptoms associated with menopause, such as hot flashes, hair loss, and cognitive reduction (3, 4).

This compound was tested in rats with Alzheimer's disease and showed improved physical health of mice. The compound also prevented the weight loss associated with the disease and improved visual spatial memory. Plaques and amyloid beta deposits in the brain were also diluted (4). Another issue that needs to be addressed in that the type of soy products affects the performance of isoflavones on brain and memory. For instance, tofu consumption

may worsen the memory status of people while soy fermentation products, like tempeh, improves the memory (3). Tempeh contains isoflavones almost twice and folate 5 times more than those in tofu. Folate itself has a protective effect on brain function and reduces the risk of dementia (3).

Conclusion

Phytoestrogens have estrogen-like properties, due to their estradiol structure, and thus in various ways, stimulate estrogen receptors, increase the survival of brain cells and prevent Alzheimer's disease. The most bioavailable phytoestrogens are isoflavones. They are shown to increase blood supply to the brain and promote recognition and memory. By their antioxidant properties, also, phytoestrogens can help prevention of neurodegenerative diseases.

Conflict of Interest

None declared.

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and increases gene expression of BDNF, TrkB receptor and synaptic factors in ovariectomized rats. *Nutr Metab.* 2010,7:75. DOI:1186/1743-7075-7-75.