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# ISOFLAVONES AND ALZHEIMER'S DISEASE: THE EFFECTS OF SOY IN DIET

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## ABSTRACT

Pathologically, Alzheimer's disease is a result of aggregation of amyloid peptides and protein tau in the brain forming neurofibrillary tangles which are highly toxic to neuronal circuits in the brain. Recent evidences report that apart from aging, estrogen deficiency is one of the risk factors predisposing to the development of Alzheimer's disease. Isoflavones, also known as phytoestrogens, are metabolized by the body forming compounds that are known to interfere with neurotoxic pathways and through their anti-fibrillization effects they play a role in reducing apoptosis of neurons and glial cells and promote axonal regeneration. Experimental studies on transgenic models with Alzheimer's disease as well as various observational and clinical trials suggest that dietary interventions with Isoflavones may have a significant role in improving portions of memory, cognition and decreasing the risk of Alzheimer's disease.

**Keywords:** Anti-oxidants; Flavonoids; Isoflavonoids; Soy; Cognition; Alzheimer's disease

## INTRODUCTION

Ageing, along with dietary habits are the major risk factors that contribute to the development of neurodegenerative diseases. Dementia is one of the types of neurodegenerative diseases. As age progresses, it leads to the loss of brain function affecting cognitive thinking, memory and behavior. Prevalence of dementia is predicted to double every 20 years worldwide and estimated to reach 115.4 million by 2050<sup>(1)</sup>. Alzheimer's disease (AD) is a form of Dementia. Pathologically, it is the aggregation of amyloid peptides and protein tau in the brain. These proteins take a form of neurofibrillary tangles which are highly toxic to neuronal pathways in the brain<sup>(2)</sup>. Evidences suggest that, apart from aging, deficiency of estrogen is also one of the factors involved in causing AD, by exposing neurons to toxic insults, including A-beta, as a result of which post-menopausal women are at a significant risk of developing AD<sup>(3,4)</sup>. Unfortunately, current drug treatments have failed to show positive results in the prevention of neurodegenerative diseases<sup>(5, 6)</sup>. Consequently, there is an increasing interest in dietary interventions. Various interventional studies have been conducted globally demonstrating the protective role of antioxidants against AD. These antioxidants include Vitamins C, E, Beta Carotene and Flavonoids<sup>(7-10)</sup>. Flavonoids belong to a group of polyphenolic compounds. These components are found in plants, and are included in human diets in the form of vegetables, cereals, tea, wine, and fruit juices<sup>(11)</sup>. The

main dietary groups of flavonoid include<sup>[1]</sup> flavonols<sup>[2]</sup> flavones<sup>[3]</sup> anthocyanidins, <sup>[4]</sup>flavanones, <sup>[5]</sup>flavanols, <sup>[6]</sup> Isoflavones<sup>(12)</sup>. Upon ingestion, these compounds are metabolized to take different forms in the body<sup>(13, 14)</sup> indirectly protecting the neuronal population from degradation, stimulating neurogenesis and augmenting neuronal functions<sup>(15-18)</sup>. Isoflavones, one of the aforementioned subtypes of flavonoids, has recently gained significant attention and is being studied extensively. Ranging from experimental studies on transgenic models<sup>(19, 20)</sup> to interventional trials using dietary supplements rich in isoflavones, it has shown to improve cognition and memory<sup>(21-23)</sup>. Isoflavones are derived from plants. So far soy-beans are the most abundant source of isoflavones while legumes, grains and vegetables are other good sources containing small amount of isoflavones<sup>(24, 25)</sup>. Chemically, isoflavones have a non-steroidal structure similar to estrogens in humans and animals, hence they are also known as phytoestrogens. In the digestive tract, the primary isoflavones (genistin, daidzin, and glycitin) are hydrolyzed into their respective aglycones (genistein, daidzein, and glycitein) which are metabolically active, before being absorbed into the system<sup>(26, 27)</sup>. There has been scanty literature about effects of Flavonoids and its subtype Isoflavones on cognitive improvement and neurodegenerative diseases. The purpose of this article is to bring together the evidence regarding positive effects of flavonoids, on cognition, and memory, particularly focusing on Isoflavones.

## Effect of Flavonoids on molecular pathways involved in Alzheimer's disease

There are several *in vitro* studies showing that green tea extract, a source of flavonoids, could protect neurons from the amyloid beta-induced damages in Alzheimer's disease<sup>(28, 29)</sup>. Researches conducted on transgenic models, focused on the processes of the amyloid precursor protein (APP) proteolysis and amyloid beta metabolism in the degenerating neurons of the brain, which is the primary pathology in Alzheimer's disease and can be possible targets in its therapy. APP can be processed by two pathways: 1) a nonamyloidogenic pathways which involve cleavage of APP to soluble APP by the alpha-secretase activity and 2) a formation of the amyloidogenic beta peptides by the beta- and gamma-secretases. Various synthetic and naturally occurring compounds have been analyzed for their efficacy in the modulation of these pathological events. Among them, epigallocatechingallate (EGCG) is able to regulate the proteolytic processing of APP both *in vitro* and *in vivo*<sup>(30)</sup>. It has been demonstrated that flavonoids could promote the nonamyloidogenic alpha-secretase pathway and reduce the formation of amyloid beta-fibrils<sup>(30)</sup>. Flavonoids also seem to have an effect on a number of intracellular signaling pathways such as mitogen-activated protein kinases (MAPKs)<sup>(31)</sup>, protein kinase C<sup>(30)</sup>, and phosphatidylinositol-3-kinase (PI-3 kinase)-Akt pathways<sup>(32)</sup>. Oxidative stress seems to be one of the major stimuli for the MAPKs cascade, which might ultimately lead to cell survival/death. MAPKs pathways play a crucial role as transducers of extracellular stimuli into a series of intracellular phosphorylation cascades. These pathways exert important role in neuronal protection against a variety of insults and are essential to cell survival<sup>(33)</sup>. *In vitro* studies demonstrate that EGCG could induce MAPKs pathways including extracellular signal-regulated kinase (ERK), c-Jun N-terminal kinase (JNK), and p38 MAPK, which protect cells<sup>(34)</sup>. For instance, in neuronal cell line and primary neuronal cultures, EGCG could prevent the decline in ERK1/2 induced by 6-hydroxydopamine or oxidized low-density-lipoproteins<sup>(35,36)</sup>, which are associated to attenuation of neuronal death and cellular injury by oxidative stress<sup>(37)</sup>.

## Effects of Soy Isoflavones on transgenic models with Alzheimer's Disease

Focusing specifically on Soy Isoflavonoids, It has been reported that the hydrolyzed forms of soybeans and isoflavones, including glycitein (Gly) and genistein (Gen), have a role in inhibiting Amyloid beta-induced apoptosis in cultured cell<sup>(38)</sup>. Mechanisms outlined by various studies include the protective effects of isoflavone-induced arginase1 activity<sup>(39)</sup>, inhibition of caspase

activation and their anti-oxidant properties which shield against the oxidative stress on the neurons<sup>(38)</sup>. Interferences in these pathways in turn reduce apoptosis of neurons and glial cells and promote axonal regeneration. Experimental studies conducted *in-vitro*, demonstrated the direct influence of isoflavonoids on proteins involved in the pathology of Alzheimer's disease. Amyloid beta solutions were prepared, which were then fibrillized. When incubated with Gly and Gen, the experiment successfully demonstrated their anti-fibrillization effects. Gly and Gen were shown to directly interact with the fibrils and inhibited the fibrillization in a dose-dependent manner<sup>(40)</sup>. Prior works on isoflavones have also shown that Gly, Gen and Daidzein (Dai), another form of hydrolyzed isoflavone to bind the monomeric form of transthyretin protein (TTR)<sup>(41)</sup> which is a protein that binds to the amyloid-beta preventing them to accumulate into plaques<sup>(42)</sup>. However the mechanisms through which isoflavones inhibit protein fibrillation are yet to be analyzed. Apart from anti-fibrillization effects, Isoflavones were reported to play a role against cell injuries caused by amyloid beta. In recent studies conducted on transgenic models, isoflavones were indicated to reduce the oxidative injury induced by amyloid beta<sup>(43)</sup>. It was also reported that Isoflavones can rescue neurons from amyloid beta induced cell death by interfering with the p38 MAP kinase pathway<sup>(44)</sup>. Mixed soy isoflavones were shown to improve parameters related to aging and Alzheimer's disease in C57BL/6J mice treated with d-galactose<sup>(19)</sup>. In another study, it was demonstrated that due to isoflavone's ability to generate PPAR- $\gamma$  expression, it can have inhibitory effects against the inflammation associated with amyloid beta in cultured neuronal cells<sup>(45)</sup>. Hence, the anti-amyloidogenic effects of soy isoflavones may be beneficial in dementia and AD and if supplemented at an earlier age, may be helpful in inhibiting or limiting the disease process. Isoflavones also possess the ability to bind to estrogen receptors. Gen and Dai bind with a greater affinity to the estrogen receptor-beta<sup>(46)</sup>. This can be linked to the fact that in the brain, there is a high concentration of estrogen receptor-beta in the hippocampus<sup>(47,48)</sup>, which might explain one of the mechanisms through which soy isoflavones benefit episodic memory.

## OBSERVATIONAL AND CLINICAL TRIALS

Humans are predisposed to neurodegenerative diseases as they age beyond 70 years<sup>(49)</sup>. Recent nutritional studies conducted on populations indicate that increased intake of fruits and vegetables are associated with improved cognition and reduced risk of senile debilitating brain diseases<sup>(50, 51, 52)</sup>. Blue-berry derived flavonoids were shown to indirectly interact with certain brain areas such as the hippocampus and dentate gyrus and

hence were associated with improvement in spatial memory<sup>(53, 54)</sup>. In a cross-sectional study conducted over 8335 subjects concluded that intake of isoflavones were inversely associated with plasma levels of C-reactive protein as well as other inflammatory markers in the blood, suggesting the anti-inflammatory role of isoflavones<sup>(55)</sup>. An observational study in a general Japanese population, investigated seven different dietary patterns and their potential association with the risk of dementia. Soybean and soybean-based products were one of the dietary patterns observed. The results revealed that a higher adherence to a diet containing high proportions of soybean and soybean products were associated with reduced risk of dementia in the studied population<sup>(56)</sup>. Most interventional clinical trials including Isoflavones were conducted on post-menopausal women. In a study, 176 post-menopausal women were supplemented with 80 mg of Isoflavones per day, followed for 6 months, revealed no significant association with better performance on neuropsychological tests<sup>(57)</sup>. Another study involved 36 post-menopausal females, were given 60mg of Isoflavones regularly in a span of 12 weeks, showed significant improvement in memory and sustained attention tasks<sup>(58)</sup>, similarly in a clinical trial, 25g of soy protein in powder or bar form containing 154 mg of total Isoflavones were administered in a population of 313 healthy post-menopausal women, for a period of 2.5 years, the results deduced that there was a significant improvement in visual episodic memory after the intervention<sup>(59)</sup>. Better mood was also observed in 78 healthy post-menopausal females after they received treatment with 60mg Isoflavones for 6 months<sup>(60)</sup>. In another study 78 elderly individuals with mild cognitive deficits were given 300mg per day of soy for 6 months, and the results concluded that treatment with soy supplementation caused a significant improvement in memory function of the elderly as compared to the placebo group<sup>(61)</sup>. Short-term studies conducted over young healthy volunteers also presented positive results. In a study, 16 young healthy females and 7 young healthy males were asked to consume 900g of soybeans for a period of 1 week. Mental Rotation and Spatial Visualization psychological tests were conducted over the volunteers during the days of the sampling. The results reported that there was a significant improvement in the Mental Rotation and Spatial Visualization psychological tests post-treatment<sup>(21,22)</sup>. Overall, clinical trials suggest that soy Isoflavones supplementation may benefit portions of memory and cognition, but less effects on global cognition. It may also prevent the decline in verbal memory observed with aging. More long-term clinical trials are needed on larger populations to detect the role of soy Isoflavones on patients diagnosed with Alzheimer's disease. Skewing the dietary

patterns towards higher proportions of soy Isoflavones may be beneficial for the population at high risk for developing Alzheimer's disease.

## CONCLUSION

In conclusion, soy Isoflavones may have a protective role against Alzheimer's disease. Experimental studies on transgenic models have shown positive effects of soy Isoflavones on the biological mechanisms involved in the pathology of Alzheimer's disease. Since most of the studies are conducted on transgenic models with scanty observational and clinical trials conducted over small sample sizes, it cannot be concluded that Isoflavones may prevent AD in high risk population. More research is needed in this area for a clinical census on the benefits of soy-derived Isoflavones.

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**Sara Habib:** Study concept and design, data collection, data analysis, manuscript writing, manuscript review

**Asad Ali Khan Afridi:** Data collection, data analysis, manuscript writing, manuscript review

**Mohammad Wasay:** Manuscript writing, manuscript review

**Romaina Iqbal:** Study concept and design, protocol writing, data collection, data analysis, manuscript writing, manuscript review