



# High intake of sunflower seeds and low mortality from Alzheimer's disease and dementia: is there a correlation?

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## Abstract

Alzheimer's disease, a progressive and irreversible neurodegenerative disorder, is the most prevalent form of dementia with an increasingly growing incidence rate worldwide. As no effective therapeutic modalities are still available for the treatment of this serious disabling condition, lifestyle modifications, especially nutritional interventions, have been shown to be important in its prevention and symptomatic alleviation. In this short perspective article, an inverse association between the intake of sunflower seeds and the mortality from Alzheimer's disease and dementia is proposed, showing that in the countries with the highest consumption of sunflower seeds, the death rate from this neurodegenerative disorder is low. The bioactive ingredients of sunflower seeds and their possible neuroprotective mechanisms are further unraveled, highlighting the potent antioxidant, antiinflammatory and neurotrophic effects of tocopherols, unsaturated fatty acids and phytosterols. Among the latter agents,  $\beta$ -sitosterol might be particularly important in combating Alzheimer's disease by enhancing the levels of nerve growth factor and thereby promoting neurite formation. If future epidemiological studies will confirm the proposed inverse association between the intake of sunflower seeds and the development of Alzheimer's disease and dementia, it is easy to include appropriate sunflower seed products in the everyday diet to protect against the pathogenesis and progression of this neurodegenerative disorder, especially in individuals with a genetic predisposition. Considering the rather long latency period before clinical manifestation of Alzheimer's disease, nutritional approaches with specific foods might be a promising strategy for fighting against dementia.

## Keywords

Sunflower seeds, Alzheimer's disease, dementia, phytosterols, molecular mechanisms, dietary intervention

## Introduction

Based on numerous epidemiological studies performed over the past decades, several associations between the higher intake of certain food products and a lower incidence of chronic degenerative diseases have been proposed. Such correlations convincingly demonstrate a preventive and protective role of one or more

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constituents of these food items against the pathogenesis and progression of severe age-related disorders. For example, the Mediterranean diet has been related to a low incidence of coronary heart diseases among the French population despite their abundant consumption of saturated fats, smoking habits and little exercise, a phenomenon known as the French paradox [1, 2]. As French people regularly drink higher amounts of red wine than other non-Mediterranean cultures, antiatherogenic effects of purple grapes' polyphenolic components, especially flavonoids, were highlighted, reducing the mortality from cardiovascular disorders and increasing the longevity [1, 3]. Also, the high consumption of soy products in Asian countries, such as Japan, China and Singapore compared to the Western regions has been associated with significantly lower incidence rate and better prognosis of hormone-dependent malignancies, including breast and prostate cancers, but also colonic tumors [4–6]. Later on, isoflavones were identified as the major anticancer components of soy-based diets [4]. In addition, the absence of age-related increments in blood pressure and hypertension disorders among Kuna Indians residing in the San Blas Islands outside the coast of Panama, despite their food salting practices, has been correlated with the large consumption of cocoa on a daily basis. Indeed, Kuna Indians drink more than five cups of cocoa per day, representing the major dietary source of calories [2, 7, 8]. These benefits were subsequently attributed to a particular subgroup of flavonoids, i.e., flavan-3-ols or catechins, providing protection against ischemic heart disease and stroke, but also diabetes mellitus and various cancer types [2, 7]. Therefore, environmental factors, and especially the diet, may play an immense role in the maintenance of a good health and protection against chronic degenerative diseases.

In this perspective article, an additional interesting association is proposed, revealing that in the countries with the highest consumption of sunflower seeds, the mortality rate from Alzheimer's disease and dementia is relatively low. On the one hand, in the two countries with the largest intake of sunflower seeds in the world, i.e., Ukraine and Russia, the consumption per capita has been reported to be much higher than the global average per year [9]. In fact, in 2015, the amount of sunflower seeds consumed worldwide was estimated to be 42 million tons, of which 11 million tons were consumed in Ukraine and 9.3 million tons in Russia, comprising 26.2% and 22.1% of global consumption, respectively [9]. On the other hand, based on the most recent data of the World Health Organization (2020), the death rates from Alzheimer's disease and dementia in Ukraine and Russia were significantly lower than the corresponding values in many other countries. In particular, the age-standardized mortality rates from Alzheimer's disease and dementia were 4.0- and 3.6-fold lower in Ukraine and Russia, respectively, than in Finland as the country with the highest dementia mortality rate in the world [10, 11]. These data clearly suggest that some bioactive constituents in sunflower seeds might possess neuroprotective properties, possibly contributing to the lower mortality rate from Alzheimer's disease and dementia.

## Sunflower seeds: their composition and health benefits

The sunflower plant (*Helianthus annuus* L.) is a leading oilseed crop that is cultivated globally, primarily for its seeds [12–14]. This annual plant belongs to the family Asteraceae and is native to Middle American region [12, 13, 15]. In Europe, its production was started in the early sixteenth century and nowadays, seeds of the sunflower plant are commercially available worldwide for their oil and protein content [12, 13]. Sunflower seeds can be used to prepare a variety of products, including cooking oil and roasted or salted snacks, whereas their nutritive value largely depends on the technology of seed processing [13, 16].

The health-promoting properties of sunflower seeds are thought to be derived from their high content of proteins, unsaturated fatty acids, phytosterols, and a wide range of vitamins and minerals [12, 13, 15]. This nutrient dense food has been found to exert a potential therapeutic action in chronic inflammatory conditions, bacterial and fungal infections, skin diseases, cardiovascular disorders and even some types of cancer [12, 13, 15]. The oil extracted from sunflower seeds is rich in unsaturated fatty acids (almost 90%), mostly oleic and linoleic acids, which can lower the risk for coronary artery disease through reducing the levels of low-density lipoprotein (LDL) cholesterol and total cholesterol. The exact fatty acid composition can differ between cultivars and vary also with environmental conditions [12–14]. In addition, sunflower

seeds contain a wide spectrum of vitamins, including vitamin E (tocopherols, predominantly  $\alpha$ -tocopherol), niacin (vitamin B3), pyridoxine (vitamin B6), pantothenic acid (vitamin B5) and folic acid (vitamin B9) [12, 13]. As potent natural antioxidants, tocopherols are involved in scavenging free radicals and preventing oxidative damage to vital cellular components, thereby exerting antiinflammatory, antiatherogenic, cardioprotective and anticancer activities [12, 13, 15]. Furthermore, sunflower seeds provide also substantial amounts of many important minerals, such as phosphorus, potassium, magnesium, calcium, zinc, iron, sodium, manganese, copper and selenium [12].

## Neuroprotective and neurotrophic effects of sunflower seeds

The neuroprotective effects of sunflower seeds have been related mainly to their high contents of antioxidant and antiinflammatory components (e.g., tocopherols and unsaturated fatty acids), which may be important in preventing and treating ischemic brain injury and stroke [15]. Intraperitoneal pre-administration of sunflower oil to experimental male mice was indeed demonstrated to reduce the brain lipid peroxidation as well as brain infarct volume and edema after the ischemic insult caused by transient occlusion of the middle cerebral artery [15]. It has been also reported that feeding rats the diet enriched with sunflower oil increased the amount of phosphatidylcholine in the brain [17]. This phospholipid is used for the formation of myelin-supporting synapse and the synthesis of neurotransmitters, thereby possibly improving memory and cognitive function [16]. Moreover, it was only very recently demonstrated that sunflower seed extract can exert neurite outgrowth-promoting activity through enhancing the levels of nerve growth factor (NGF) in rat pheochromocytoma cells PC12 [16]. As NGF supports the survival, differentiation and maintenance of neurons, its age-related decrease in the brain is thought to be one of the major causes of Alzheimer's disease. However, the administration of NGF as a medicine is complicated due to its inability to pass the blood-brain barrier (BBB). Therefore, low-molecular weight lipophilic compounds with the NGF-enhancing activity might be valuable in postponing the Alzheimer's disease onset and improving its symptoms [16]. Certain phytosterols, especially  $\beta$ -sitosterol, were found to be responsible for the neurite outgrowth-promoting activity of sunflower seed extract, showing that these neurotrophic compounds might present candidate constituents for the prevention of Alzheimer's disease and dementia through the high dietary intake of sunflower seeds [16]. It was indeed previously reported on a mouse model that  $\beta$ -sitosterol can penetrate the BBB and accumulate in the brain cells [18].

It is clear that further preclinical studies are required to unravel the molecular mechanisms under neurotrophic and neuroprotective effects of bioactive agents in sunflower seeds, hopefully leading to the initiation of clinical trials in the near future to test the molecular leads against neurodegenerative disorders. However, most importantly, the large-scale epidemiological studies, both prospective cohort studies as well as case-control studies, would be needed to determine the statistical strength behind the proposed inverse association between the dietary intake of sunflower seeds and the pathogenesis and progression of Alzheimer's disease and dementia. If this inverse correlation will be confirmed, it can be of great importance for the public health policies in the management of dementia around the world.

## Alzheimer's disease as a potential target for sunflower seeds

Alzheimer's disease is a serious global health challenge [16]. Being the most common form of dementia, it accounts for 60–80% of all cases [19, 20]. According to the data of Alzheimer's Disease International, more than 55 million people around the world lived with dementia in 2020, whereas the number of patients almost doubles every twenty years, reaching 139 million in 2050, mostly due to the aging societies and an increase in the average life expectancy [16, 19, 20].

Alzheimer's disease is a progressive and irreversible neurodegenerative disorder, characterized by a decline in cognitive and functional abilities, episodic loss of memory, language and problem-solving skills, neuropsychiatric symptoms and premature death [19, 20]. The incidence and prevalence of this disease are largely affected by the genetic predisposition of an individual, along with his or her exposure to different environmental risk factors [20]. Although the exact causes of Alzheimer's disease have still remained to be

clarified, this condition manifests mainly as the accumulation of amyloid beta peptide plaques and the formation of neurofibrillary tangles of tau protein in the brain, besides the decrease in NGF levels, neuronal loss, synaptic changes, neuroinflammation and neurovascular dysfunctions [16, 19, 20]. Currently, no effective treatment options to reverse this situation are available and the adverse effects of pharmacological agents can further worsen the patient [16, 19]. However, as environmental factors such as viral and bacterial infections, exposure to heavy metal ions, poor dietary habits, sleep disorders, altered gut microbiota, an excessive psychological stress and anxiety can all contribute to the pathogenesis of Alzheimer's disease, appropriate lifestyle modifications may be important in the fighting against dementia [20]. In particular, nutritional interventions have been shown to be effective in slowing down the progression of Alzheimer's disease and improving cognitive function, with the Mediterranean diet, ketogenic diet, supplementation with polyunsaturated fatty acids and probiotics highlighted as beneficial measures. An adequate status of vitamins and minerals has also been reported to be crucial [19]. On the contrary, the Western dietary pattern characterized by a high intake of saturated fats, red and processed meat and refined sugars presents a risk factor for neurodegeneration by increasing the levels of inflammatory mediators [19, 20].

In the current perspective article, it is proposed that inclusion of sunflower seeds in the everyday diet might also be an important nutritional strategy for preventing and postponing the onset of Alzheimer's disease and cognitive decline, mainly in virtue of their high content of specific phytonutrients, such as unsaturated fatty acids, tocopherols and phytosterols. This approach could be especially useful in individuals with genetic predisposition to Alzheimer's disease, most importantly those harboring the  $\epsilon 4$  allele of apolipoprotein E (*Apo E*) gene [19, 20]. Recently, it was found that a two-month oral administration of sunflower seeds (50 mg/kg body weight) in combination with black mulberry fruit extract and pumpkin seeds in healthy young adults led to an improvement of memory function. This was accompanied by enhancing the production of neuroplasticity marker (brain-derived neurotrophic factor) and lowering the secretion of stress hormone (glucocorticoid receptor- $\alpha$ ) [21]. The reported evidence on promotion of memory performance may be valuable in designing further clinical studies.

Although sunflower seeds are natural products with many described health benefits, it has to be born in mind that an excessive intake of these seeds may be associated also with some potential health risks. As sunflower seeds are a rich source of omega-6 polyunsaturated fatty acids, their overconsumption may result in an imbalance with omega-3 fatty acids in the human body, thereby contributing to the development of oxidative stress and chronic inflammation [22].

## Conclusions and further perspectives

The prevention of Alzheimer's disease and dementia, delaying the onset of symptoms and slowing down the cognitive impairment are critical not only from the individual point of view, but considering the aging population in general, the increasing incidence rate of patients will also be a huge economic burden for diverse societies worldwide. This involves the expenses related to caregivers' labor force, various supporting services and auxiliary means, but also the loss of working years due to disabilities, not to mention the psychological and emotional sufferings to patients themselves and their relatives [16, 20]. Therefore, the development of effective preventive measures and therapeutic modalities against neurodegeneration is an urgent global task. If further epidemiological studies will confirm the proposed association between the high intake of sunflower seeds and the low mortality from Alzheimer's disease and dementia, it would be easy to include some amounts of this food in the everyday diet, for example through addition it to bread or biscuits by supplementing wheat flour [13]. This is especially convenient, taking into account the low cost and broad accessibility of sunflower seeds [12]. Moreover, as the temporal lag between the development of the first biochemical changes in the brain and the clinical manifestation of Alzheimer's disease may be about 10–15 years, a rather long period is made available for the intervention with effective nutritional strategies to delay the cognitive decline and dementia, thereby improving the quality of life in senescence [20].

## Abbreviations

NGF: nerve growth factor

## Declarations

### Author contributions

KS: Conceptualization, Methodology, Writing—original draft, Writing—review & editing.

### Conflicts of interest

The author declares that there are no conflicts of interest.

### Ethical approval

Not applicable.

### Consent to participate

Not applicable.

### Consent to publication

Not applicable.

### Availability of data and materials

Not applicable.

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