Review on: Contribution of Nutrients to Retard the Progression of Alzheimer's disease

By

Bithi Rani Saha

Student ID: 16346054

Bachelor of Pharmacy (Hons.)
School of Pharmacy
BRAC University
November 2022

Declaration

It is hereby declared that

1. The thesis submitted is my own original work while completing degree at BRAC University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I have acknowledged all main sources of help.

Student's Full Name & Signature:

Bithi Rani Saha

16346054

Approval

The thesis titled “Contribution of Nutrients to Retard Alzheimer’s Disease” submitted by Bithi Rani Saha (16346054) of Summer, 2020 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy.

Supervised By:

_____

Dr. Md. Aminul Haque
Designation
School of Pharmacy
BRAC University

Approved By:

Program Director:

_____

Professor Dr. Hasina Yasmin
Program Director and Assistant Dean
School of Pharmacy
BRAC University

Dean:

_____

Professor Dr. Eva Rahman Kabir
Dean
School of Pharmacy
BRAC University

Ethics Statement

This study does not involve any human or animal trial.

Dedication

Dedicated to my parents

Abstract

In neurology, Alzheimer's disease represents greatest unmet medical need. Formation of neurofibrillary tangles, Amyloid Beta-peptide (Aβ) deposition, and significant oxidative stress, synapse loss are features of the brain in alzheimer's disease. Although current treatments lessen symptoms, they do not dramatically change how the disease develops. However, a number of strategies to halt the progression of the disease have moved to clinical trials in recent years. The most sophisticated of these focus on amyloid-peptide and tau protein and clearance, reducing oxidative stress which is a hallmark of alzheimer's disease and is thought to contribute to the development of disease. At this moment, Pharmacological treatments for alzheimer's disease are just partial inhibitors rather than curative. Therefore, nonpharmacological therapies may be essential to halting or delaying the onset of the illness; diet in this contextis validated by a substantial amount of research. In this review, some theoretical and practical ideas regarding significance of nutrition to cure alzheimer's disease have been analyzed.

Keywords: Alzheimer’s disease; aementia; amyloid-β; neurofibrillary tangle; tau protein; aiet; nutrition.

Acknowledgement

The first and foremost praises and thanks to God for his shower of blessings throughout my research work to successfully complete my work. I would like to express mydeep and sincere gratitude to my thesis supervisor Dr. Md. Aminul Haque, Assistant Professor, School of Pharmacy, BRAC University. He has provided a great support to complete my project through her expert supervision and guidance through the project by sharing her valuable knowledge. Next, I want to acknowledge Dr. Eva Rahman Kabir, Dean, School of Pharmacy, Brac University. I am very grateful to have her as our chairperson. Last but not least I am thankful to both of my project group mates for being very helpful throughout the time.

Table of Contents

List of Tables

List of Figures

List of Acronyms

AD	Alzheimer's Disease
LOAD	Late Onset Alzheimer's Disease
ApoE	Apolipoprotein E
T2DM	Diabetes Mellitus
ROS	Reactive Oxygen Species
NFT	Neurofibrillary Tangles
MCI	Mild Cognitive Impairment
AGE	Advanced Glycation End product

Chapter 1

Introduction

Alzheimer’s disease

Alzheimer's disease (AD) is a progressive neurological condition associated with ageing that causes memory and cognitive impairment and is the dementia's root causes in older individuals.Alzheimer's disease (AD) progresses by first causing widespread memory issues, then a slow loss of cognitive function that causes people to become bedridden and dependent on care, and ultimately results in death nine years after diagnosis(Citron, 2010). In this case, selective brain regions experience the buildup of aberrant protein deposits, such as extracellular amyloid plaques, intracellular neurofibrillary tangles (NFT), and synaptic loss (Pocernich et al., 2011).Every five years beyond the age of 60, the prevalence of AD doubles, rising from 1% among those ages 60 to 64 to up to 40% among those ages 85 and older. Women are 1.2 times more likely than males to be familiar with the illness. An estimated 360 000 new cases are reported annually, which works out to 980 new instancesdaily or 40 new cases each hour(Cummings & Cole, n.d.). In 2015, it is estimated that throughout the world 44million people had been diagnosed with AD and this figure will be doubled by 2050. Many identified genes involved with the disease. The most frequent form of AD is late onset (LOAD)and its pathology includes environmental factors as well as genetic predisposition and Over 95% of patients are carrying this LOAD. Some of these genes alone are associated with the early beginning of the disease with a direct causative influence. On the other hand, certain unexplained genes may determine vulnerability in late-onset types. 5% of patients have another kind of Alzheimer's disease, which is brought on by alterations in the genes for presenilin 1 and 2 (PSEN-1 and PSEN-2) on chromosomes 14, 1, and the amyloid precursor protein gene on chromosome 21.

History

German psychiatrist and neuropathologist Dr. Alois Alzheimer first introduced and explained about the neurodegenerative disease which is named after him called Alzheimer's disease more than 100 years ago (Deture & Dickson, 2019). In 1901, he was working as a psychiatrist in Frankfurt, where a 51-year-old woman who suffered from depression, paranoia, delusional thinking, hallucinations, and dementia was admitted for treatment. As the years went by, he became increasingly obsessed with the patient. Dr. Alzheimer recognized that she exhibited signs and symptoms that were not familiar to him and were not previously described in the literature. She died in April 1906 at the age of 55. As part of his research at Emil Kraepelin's laboratory, Alzheimer brought the patient's brain to Munich, where he examined her tissue under a microscope and identified neurofibrillary tangles and amyloid plaques. Later he described the features of amyloid plaque and neurofibrillary tangles; those are mainly functions for AD and required for this disease pathological diagnosis. He described the pathology and symptoms of presenile dementia in a brief lecture at the Tubingen meeting of the Southwest German Psychiatrists entitled "On the Peculiar Disease Process of the Cerebral Cortex" (Knopman et al., 2019). Dr. Kraepelin's mention of Alzheimer's disease in a textbook would make the name famous. By 1911, physicians in the U.S. were using Alzheimer's descriptions of this particular type of dementia to diagnose patients.

Epidemiology

There is yet to be a randomized clinical trial to support any specific dietary modification, and no specific environmental contaminant has been reliably linked to AD. Research has found connections between traumatic brain damage, epidemiological depression, and other factors. The chance of developing a disease is increasing due to factors influencing the cardiovascular and cerebrovascular systems, such as cigarette smoking, obesity, and midlife high blood pressure. On the other hand, anti-inflammatory drugs (such as those used to treat arthritis and diabetes) appear to reduce AD risk. Some research even suggests that it has a positive impact. According to some research Psychological and social aspects (for example, education, physical exertion and mental activity) has some beneficial impact (Goddard & Turner, 2014).

Etiology

One-fifth of cases are familial, and genetic factors play a crutial role in them. Early-onset conditions with autosomal dominant inheritance and a later-onset group with polygenic inheritance are the two primary groups of familial instances. One of the apolipoprotein (apoε4) alleles is inherited more frequently in heterozygotes (2-4 times) than homozygotes (6–8 times) and is related to a higher risk of getting the illness. However, it is not clinically beneficial because its presence is neither essential nor sufficient for the onset of the illness (Goddard & Turner, 2014). In AD, the hippocampus and cerebral cortex in particular show macroscopically atrophic changes in the brain. Histologically, the cerebral cortex develops neurofibrillary tangles and senile plaques, which are symptoms of the disease. The plaques often test positively for the protein ubiquitin, which targets undesired or damaged proteins for destruction. Histochemical staining shows substantial amounts of amyloid in the plaques. As a result, it has been hypothesized that the illness may be brought on by flaws in the neuronal cells' capacity to break down undesirable proteins (Knopman et al., 2019). There have also been several reports of neurotransmitter disorders. While anomalies of noradrenaline, 5-HT, glutamate, and substance P have also been identified, there is a specific impairment of cholinergic transmission (Goddard & Turner, 2014).

Pathology

Neuritic plaques and neurofibrillary tangles must be present in greater numbers than would be expected in age-matched healthy controls, according to current pathologic criteria for the diagnosis of AD. Microglia, astrocytes, and dystrophic neurites, which commonly feature paired helical filaments, surround an amyloid protein core in neuritic plaques. The second important histologic component of AD is neurofibrillary tangles (“2020 Alzheimer’s Disease Facts and Figures,” 2020).They have paired, abnormally phosphorylated tau protein helical filaments that occupy the cell body and extend into the dendrites. Reduced synaptic density, neuronal loss, and granulovacuolar degeneration in hippocampal neurons are additional characteristics of AD in addition to the two primary classic histopathologic indications. Cholinergic, noradrenergic, and serotonergic transmitter deficits are caused by neuronal atrophy or loss in the locus coeruleus, locus basalis, and raphe nuclei of the brainstem (Norwitz et al., 2021).

Risk Factors

It's crucial to identify the elements influencing AD to reduce the likelihood of a future in which the illness affects a large proportion of the population. Numerous epidemiological studies published in recent years have focused on the definition of AD risk factors. Genes associated with susceptibility and environmental variables are two categories of risk factors for LOAD. Apolipoprotein E (ApoE), which contains a substantial genetic component and leads to LOAD, is currently the most researched genetic risk factor for AD. This apolipoprotein E (ApoE) is created by the liver, macrophages, and nervous system (CNS). The sources of this chemical are astrocytes and microglia in the CNS (Hu et al., 2013).

Nevertheless, in specific pathological circumstances, stress or neuronal damage might trigger the production of ApoE in neurons (stressors and injurious agents). Obesity, hyperhomocysteinemia, hypertension, and type 2 diabetes mellitus are the key metabolic and nongenetic risk factors (T2DM).

Genetic Propensity to LOAD

A family of proteins called apolipoproteins transports and binds lipids in the lymphatic and circulatory systems, where they are involved in maintaining lipid homeostasis. ApoE has a clear connection to the pathogenesis of LOAD, as evidenced by research. Among 29 amino acids ApoE is a glycoprotein. The structure of the glycoprotein apoE, which has 299 amino acids, varies according to genetic differences (Grill & Cummings, 2010).

LOAD-Related Nongenetic and Metabolic Risk Factors:

1. **Hypercholesterolemia**

As a potential risk for AD, high serum and blood lipid profile have been proposed. In an experimental cell-based investigation, it was discovered that the distribution of cholesterol in the membrane had an impact on the APP's metabolism and movement, the functions of α-, β-, γ-secretase, and Aβ synthesis (Power et al., 2019). Althoughthere is yet no clear understanding of how cholesterol alters the metabolism of Aβ, it is known that variations in cholesterol levels affect cell membranes by impairing lipid rafts, membrane micro domains important for protein transport, signal transduction, and neurotransmission. These cholesterol-rich lipid rafts are where the final step in the creation of the Aβ peptide, the γ- secretase cleavage of APP, takes place (Grill & Cummings, 2010).

2. **Hyperhomocysteinemia**

Pharmacological evidence demonstrates that homocysteine enhances the inflammatory process, lipid buildup, and N-methyl-D-Aspertate receptor (MMDA) activation. In AD models, it has been demonstrated that NMDA receptors regulate the Aβ peptide's downstream effects, and the harmful impact of Aβ is eliminated by pharmacologically suppressing the activation of this receptor (Solomon et al., 2014).

3. **Hypertension**

Many studies have established a relationship among hypertension and AD by connecting the disease to brain atrophy and the production of NFTs. This relationship, nevertheless, varies with age and is complicated. It has been established that having elevated blood pressure in early adulthood increases the likelihood of developing AD, despite some research finding no correlation with dementia and hypertension in the seniors (Otaegui-Arrazola et al., 2014).

4. **Obesity**

Numerous studies have discovered obesity is an elevated threat to cognitive deterioration, AD, and inflammation of the CNS because of enhanced proinflammatory cytokines. According to researches utilizing both human and animal models, several dietary elements may be essential in lowering the prevalence of AD. For instance, a diet heavy in fats is linked to obesity, resulting in a higher chance of AD (Polidori, 2014).A recent study found that a high-fat diet can cause damage comparable to the pathology connected to Alzheimer's disease, including potentiation of the APP's β-secretase processing, cognitive loss, and mitochondrial damage related to insulin resistance.

5. **Type 2 Diabetes Mellitus**

Type 2 diabetes mellitus (T2DM), a disorder that is similarly widespread and regarded to be a separate risk factor for AD, is linked to ageing, obesity, and other prevalent conditions. Vascular lesions, oxidative stress, inflammation, elevated glycolysis end products, abnormal insulin receptor signaling, insulin resistance, insulin degradation and its connection to a protein deposits are a few of the theories that have been put forth regarding the link between diabetes and dementia (Kamphuis & Scheltens, 2010).

Chapter 2

Nutrition and Alzheimer's Disease

Evidence that links nutrition to mental health supports the critical role that nutrients play in maintaining healthy brain function, including cognition, memory, mood, and general mental well-being. Brain functions may be changed in cases of dietary deficiencies, particularly during senescence, encouraging the development of neuropsychiatric illnesses (de Wilde et al., 2017). Therefore, the quality and amount of nutrient intake, as well as their capacity to cross the Blood Brain Barrier, biological utilization, and absorption all affect how the brain functions.

Energy State, Nutrients and Brain

Energy State

Energy state and energy intake are connected, and hormones and growth factors regulate both of these processes. These chemicals alter gene expression involved in brain growth and function. The body's energy level controls synaptic plasticity, neurotrophic factor gene regulation, and metabolic processes related to mitochondrial energy metabolism that are associated with mental health. The accumulation of Aβ in AD is connected to reduction in mitochondrial biogenesis, which leads to mitochondrial dysfunction and interference with energy metabolism (Grant, 2014).

Carbohydrates

The cholinergic system is likely how glucose contributes in some measure to the control of learning and memory formation processes. Memorization has been demonstrated to suffer when blood glucose levels are not properly controlled; for instance, mild hypoglycemia causes general cognitive dysfunctions. Raised insulin levels may contribute to the relationship between reduced memory, attention, and other cognitive functions in people with diabetes mellitus and their healthy counterparts (Seneff et al., 2011).

Insulin is involved in brain growth, survival, and neuroprotective activities and is assumed to play a regulatory role in the gene expression associated with long-term memory. In fact, it was shown that the fasting blood sugar (FBS) level beyond the usual range are associated

with higher damage in the hippocampus and amygdala in cognitively healthy non-diabetic people.

Dysregulation of brain glucose has been linked to the etiology of AD. Even in the period before the onset of the disease, there was a significant concentration of glucose in the brain areas more prone to the aggregation of Aβ and hyperphosphorylated tau, which sequentially increases the severity of these conditions. Additionally, this dysregulation has resulted in brain damage due to neuronal dysfunction in the endoplasmic reticulum and insulin signaling (Muñoz Fernández & Lima Ribeiro, 2018). Fig.1 depicts how these claims relate to the development of AD and the glucose metabolism's possible importance.

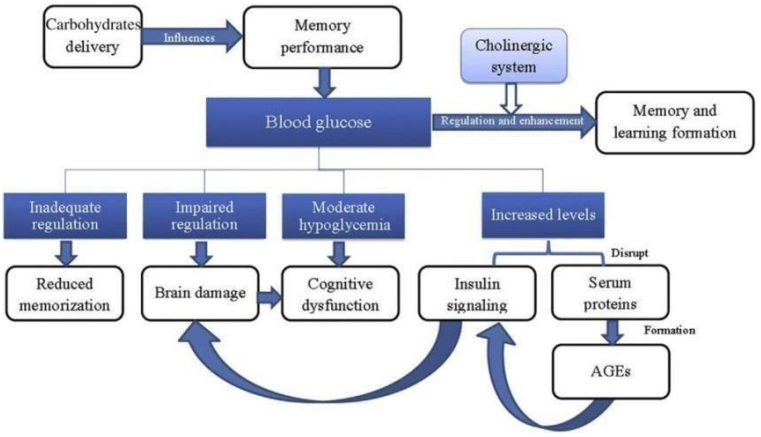

Figure 1: Diagram showing the effects of glucose on AD-related brain alterations (Muñoz Fernández & Lima Ribeiro, 2018).

Amino Acids and Proteins

Amino acids (AAs) and their derivatives are essential for the correct functioning of the central nervous system (CNS). Dietary protein deficiency causes mental health issues such as altered cerebral monoaminergic activity, which may have an impact on diseases mediated by neurotransmitters and psychosocial behaviour. The hippocampus and the cortex appear to be the two parts of the brain that are more prone to this impairment. One of the biggest neutral AAs with a modulatory function in behavioural and sleep processes is tryptophan, which serves as the main substrate for the catecholamines and serotonin synthesis. Tryptophan deficiency may occur before mental and emotional disorders. According to certain experimental evidence, dietary tryptophan intake may increase serotonin levels, hence protecting against Aβ buildup in the hippocampus (Suárez et al., 2019). The Aβ aggregation in AD may have an impact on the synaptic concentrations of glutamate, an excitatory

neurotransmitter, which is known to disrupt glutamatergic neurons because of its involvement in learning and memory.

The generation and distribution of acetylcholine may be stimulated by the L-carnitine derivative acetyl-L-carnitine (ALC). ALC was discovered in nonhuman investigations to enhance brain synapse function, hence enhancing memory and learning ability under aging settings. According to research, ALC enhances spatial learning and long-term memory performance, raises neurotrophin levels and changes their activity, and lowers homocysteine levels, tau hyperphosphorylation, and Aβ accumulation in mice. The main endogenous antioxidant, glutathione, is a precursor to a cysteine derivative N-acetylcysteine (NAC).NAC's antioxidant activity in animal models contributes to its positive effects by halting oxidative processes (Śliwińska & Jeziorek, 2021).

Fatty Acids and Lipids

To protect the central nervous system (CNS) from oxidative stress and inflammation, polyunsaturated fatty acids (PUFAs) may be beneficial. DHA was shown to have the capacity to decrease Aβ synthesis in animal models and cultured cells by suppressing Aβ-42-induced neurotoxicity and enhancing microglial phagocytosis of Aβ-42, boosting brain cellshielding them from amyloidosis-related cell death and ensuring their survival. Despite being recognized for being prone to oxidation, n-3 PUFAs have been proven in-vivo and in-vitro studies to exhibit antioxidant properties due to the decreased generation of reactive oxygen species and lipid peroxidation metabolites (Muñoz Fernández & Lima Ribeiro, 2018).

Numerous studies suggest that other lipids indirectly contribute to the pathophysiology of AD. Although cholesterol is essential for synaptogenesis and neurotransmission in the membranes of brain cells, excessive levels have been linked to Aβ formation in neural tissues and may be associated with AD through vascular dementia (Kim et al., 2015). However, high levels of total and low-density lipoprotein cholesterol have been associated with enhanced cognition and memory in elderly individuals without dementia.

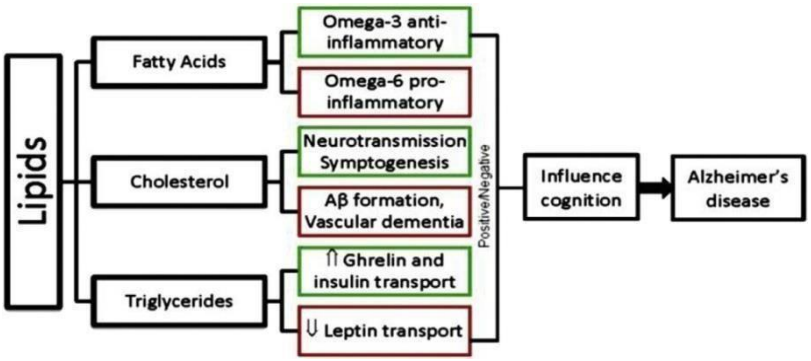

Figure 2: Schematic depiction of lipids in brain changes associated with AD (Muñoz Fernández et al., 2017).

On the other hand, triglycerides have been linked to decreased leptin transport through the BBB. Leptin is a hormone that affects the hippocampus and is believed to have a favorable impact on memory and learning processes. Additionally, it improves ghrelin and insulin transportation, which may benefit cognition even in AD. High levels of triglycerides in adulthood have also been linked to the development of neuropathology two decades later in cognitively healthy people, according to research (Fig. 2).

Micronutrients

A macronutrient's ability to be metabolized depends on the proper ratio and amount of micronutrients, primarily vitamins and minerals. According to Table 1, certain of these micronutrients are particularly important for AD neuropathology and brain function.

Micronutrients	**Functions in Brain**	**Food Sources**
Vitamin A and Beta-carotene	Inhibit formation of Aβ oligomers and neurofibrillary tangle.	oily fish, cheese, eggs, milk, fortified low-fat spreads, and yogurt (Vitamin A). Turmeric, green leafy vegetables such as carrots, spinach, red peppers, and sweet potatoes(beta-carotene).
Vitamin C (Ascorbic Acid)	Reduce oxidative stress and Aβ oligomer formation.	Citrus fruit such as oranges and orange juice, peppers, sprouts, potatoes, strawberries, blackcurrants, broccoli.
Vitamin E(α-tocopherols)	Provide neuroprotection by inhibiting oxidative stress. Aβ associated free radicals	Pumpkin, red bell pepper, sunflower, soybean oil, sunflower seeds, almonds, peanuts, peanut butter.

	scavenger.	
Polyphenols	Decrease homocysteine concentration. Inhibit inflammatory response, modulation of enzymes, Aβ formation.	Cinnamon, green tea, flaxseeds, olives, barriers.
Vitamin B (folic acid, B6, B12)	Reduce concentration of homocysteine. Inhibit oxidative stress. Controls Aβ and tau phosphorylation.	Chickpeas, kidney beans, broccoli, spinach, cabbage, liver.
Iron	Mediate oxidative stress.	Soybean flour, red kidney beans, chickpeas, nut, dry fruits.
Magnesium	Protect synaptic plasticity.	Dark green leafy vegetable, dried beans, legumes, low fat milk, dried nuts and yogurt.
Zinc	Decrease Aβ and tau pathology in hippocampus. Reduce hippocampus dependent memory deficit.	Fishes, seafood.
Selenium	Modulate brain functions. Inhibit neuronal apoptosis.	Bread, serials, egg, brazil nut.

Table 1: Micronutrients and their functions in brain (Barnard et al., 2014a; Hu et al., 2013)

Other Dietary Substances May Ward off AD

Along with the basic nutrients, attention has been generated by several food-based molecules' anti-inflammatory and antioxidant capabilities. In this article, we highlight compounds that might possibly help prevent or lessen AD. These substances have a connection to the control of inflammation and the gut environment.

Prebiotic, Probiotic, and Symbiotic Substances

It is reasonable to believe that prebiotics, probiotics and symbiotic compounds may be crucial to preventing, delaying, or minimizing some of the signs of AD in light of the inflammatory hypothesis. Numerous in vitro or animal investigations have provided conclusive proof of the link between gastrointestinal and brain abnormalities in AD. However, so far, there has only been one modest clinical investigation with people. Probiotics were tested for their effects on AD patients by Akbari and colleagues. Consuming Lactobacillus and Bifidobacterium for 12 weeks lowered oxidative stress, insulin resistance, serum lipids, and mental status as assessed by the Mini-Mental State Examination when compared to a control group (Muñoz Fernández et al., 2017).

Polyphenols

Polyphenols are ubiquitous molecules that are present in various foods, primarily vegetables and fruits. Several aspects of brain activity are impacted by their metabolites, including (1) involvement with neuronal/glial signaling pathways; removal of free radicals; chelation of metals; and activation of proteins and enzymes involved in synaptic plasticity and neuronal repair; (2) enhanced cerebral blood flow; (3) blocking of pathological processes in certain brain areas; and (4) involvement with neural signaling pathways involved in programmed cell death and cell survival. The majority of these studies were conducted in vitro or with nonhuman models (Miranda et al., 2017). Finally, some research suggests that taking a polyphenol supplement may help to improve intestinal microbiota.

Nutritional Management for Patient with AD

The body weight loss caused by many sources, once the disease is established, is one of the key issues in its care. Some of these causes include olfactory and taste problems, medial and temporal lobe atrophy, cognitive, behavioral, and motor impairments, and olfactory and behavioral disorders. In addition, secondary considerations include comorbidities, social circumstances, and drug side effects. Remembering to eat, refusing to eat, rising energy expenditure, and losing appetite are all related to these aspects.

Possible Strategies to Minimize Symptoms of AD through Food according to the Stages of the disease.

Disease stages	Factors relating to food consumption	Possible ways to reduce symptoms
Initial	lower thresholds for thirst and test sensitivity	The joy of eating may be increased by using herbs and spices. The individual can gain from participating in meal preparation, even with minor duties. It's crucial to encourage drinking of water. It is possible to utilize a food diary as a tool for cognitive training. (For instance, a journal where they record their meals and certain memories that certain foods may evoke).The patient may be helped to avoid dieting if they practice in social groups. (such as those hosted by community centers, family and friends)
Intermediate	Meals are frequently forgotten by patients; they eat, but nearly instantly forgot. More commonly dysphasia happens.	To combat forgetfulness, it may be a good idea to divide your meals into smaller portions throughout the day. It is crucial to continue eating meals as a family, despite how challenging it might be, in an effort to lessen or delay forgetting. The requirement for thickeners must be understood, and the meals' consistency must be carefully considered. Using flavored water with mint, lemon or orange peel, cinnamon, or other flavors, among others, seems to be beneficial.
Advanced stage and palatable care	Apathy and complete cognitive Impairment define this stage of the illness. Feeding is linked to a significant risk of hypoxia and bronchoaspiration. Typically, the patient is unable to feed	A helpful tactic is to eat alongside the patient while replicating the mouth movement for them. As a result of significant risk of dysphasia at this stage, eating calls for extra care. Consider a diet with a gummy consistency

	himself, when feed is in the mouth, it's normal for people to forget purpose of their cutlery and be unsure of what to do next.	and thickened beverages at the terminal period. It is crucial to take nutritional supplements like hyper caloricinto account.

Table 2: Food intake according to stages of AD to minimize symptoms (Muñoz Fernández & LimaRibeiro, 2018).

AGE and Alzheimer's Disease:

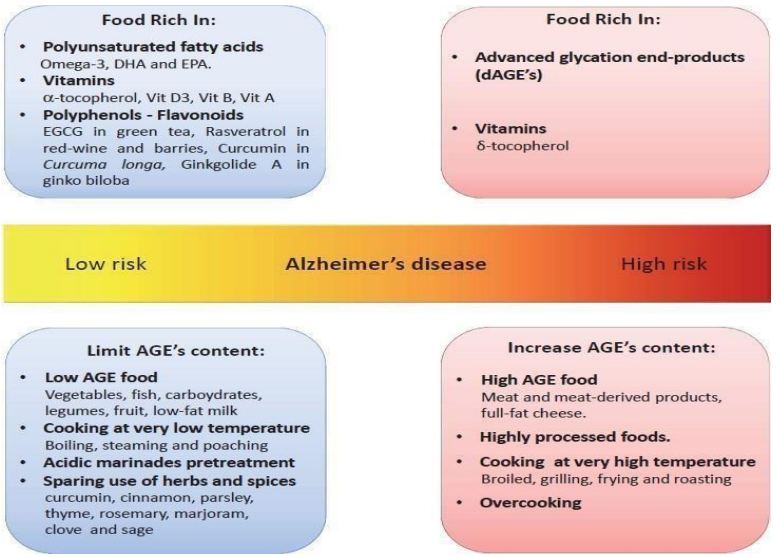

Figure 2: Diet and cooking techniques in the fight against Alzheimer's disease (Abate et al., 2017).

In neurological diseases and chronic illnesses, a high-AGE diet raises oxidative stress and proinflammatory markers. A risk-modifying factor for the pathogenesis of Alzheimer's disease is high AGE. Regarding establishing the upper threshold of dietary AGE consumption or defining the range that is appropriate, there are currently no specific rules available. When chicken breast is cooked, it has 1,000 KU of AGE, but when it is grilled, the amount might reach 9,000 kU. The polyphenols found in cooking herbs like sage, marjoram, tarragon, and rosemary have been shown to be potent inhibitors of protein glycation. Meat can be cooked with an acidic ingredient like vinegar or lemon juice to avoid the production of AGEs (Seneff et al., 2011).

Chapter 3

Treatment to prevent AD

Pharmacological Treatment

As a neurodegenerative ailment associated with aging that is incurable, Alzheimer's disease needs an accurate diagnosis that is made as early as possible. It also demands sufficient etiological therapy. Prevention is a superior approach to this public health issue because therapy alternatives have mostly focused on symptom relief and slowing the rate at which damage is progressing. Despite this, the illness has not been dramatically reversed. It is believed that the spread of the illness is facilitated by toxic forms of tau or Aβ, and that inhibiting the production of these peptides may contribute to effective therapies. The current therapy for this dementia has concentrated on cholinesterase inhibitors and a glutamate antagonist, which only give symptomatic relief even though basic and clinical research has demonstrated that it is multifaceted and has several causal elements (Solomon et al., 2014).Clinical studies are presently being conducted to test etiology-based therapies, which will complement existing preventative measures including comorbidity management, healthy eating, exercise, and cognitive stimulation.

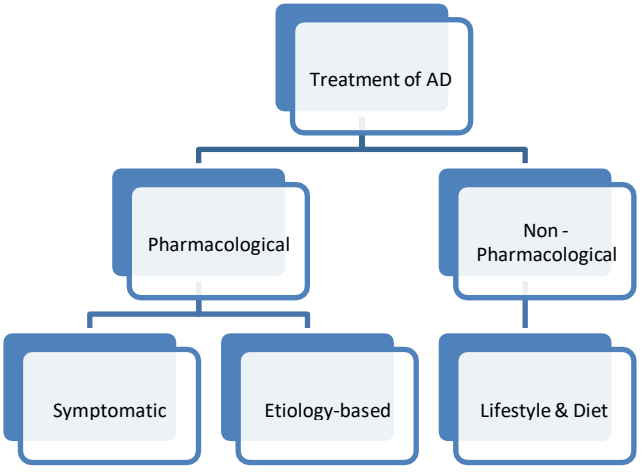

Figure 4: Hierarchy of AD Treatment

1. Symptomatic Treatment

(a) Acetylcholinesterase Inhibitors.

The vital function acetylcholine (ACh) plays in mediating memory and learning is well-known. As a result, cholinesterase inhibitors are an effective form of therapy for AD. Rivastigmine, donepezil, and galantamine are prescription drugs that raise levels of acetylcholine (ACh) and improve cholinergic function in the brain by blocking the action of the enzyme acetylcholinesterase (B. Pocernich et al., 2011).

(b) N-Methyl-D-aspartate Receptor (NMDA) Antagonist

In mild-to-moderate AD, the NMDA receptor antagonist memantine has a marginally positive impact on cognition. By reducing GSK-3 activity, which in ultimately decreases tau phosphorylation, it can counteract this overstimulation. Acetylcholinesterase inhibitors can be taken with memantine or administered alone (Mendiola-Precoma et al., 2016).

2. Etiology-Based Treatment

The major risk factor for sporadic AD is aging, but secretases and kinases engaged in the hyperphosphorylation of tau protein are being targeted.

(a) Secretase Inhibitors

The APP molecule is initially broken by either β-secretase or γ-secretase enzymes, and the resultant fragments are subsequently processed by α-secretase. The application of inhibitors for this amyloidogenic pathway has been supported by the concept of "over-activation" of β- and γ-secretases or age-related reduced α-secretase functioning (Doraiswamy & Xiong, 2006).

(b) Amyloid Binders

Concentration-dependent Aβ deposition in AD may be caused by enhanced APP amyloidogenic processing and ineffective peptide elimination. The ApoE determinant and decreased activity of A-degrading enzymes, such as the insulin-degrading enzyme neprilysin, are consistent with the notion that AD is a metabolic disease (Mendiola-Precoma et al., 2016).

(c) Anti Aβ aggregation compounds

Epigallocatechin-3-gallate is one type of small molecule inhibitors of Aβ aggregation being investigated in therapeutic trials. Others are also being investigated for potential clinical applications, including tramiprosate (phase III), clioquinol (phase II), scylloinositol (phase II), and others ((Doraiswamy & Xiong, 2006)).

(d) Tau Therapies.

One of the goals of this treatment is to prevent clusters of tau filaments that are coupled and helically twisted in neurofibrillary tangles. Clinical trials for immunotherapy began with the administration of AADvac1, and now research for ACI-35 (an additional liposomal-based vaccine) has begun (Weller & Budson, 2018).

Nonpharmacological Treatments

The use of nonpharmacological therapies as adjuvants in other types of therapy or for the prevention of AD is crucial. The approaches to preventing AD can be split into two categories: lifestyle approaches and food and pharmacological approaches.

Lifestyle and dietary guidelines

Daily basis, individuals suffering from Alzheimer's needs to select their diet and way of life based on the best current research. At a meeting in Washington, D.C., research on the effects of dietary components, physical and mental activity, and sleep on various areas of cognition was reviewed (Barnard et al., 2014a).

Some important guidelines as follows:

- Vegetables, legumes (beans, peas, and lentils), fruits, and whole grains should take the place of meats and dairy products as the major ingredients of the diet.
- Reduce consumption of trans and saturated fats.
- Choose vitamins without iron and copper if a patient is taking more than one, and only take iron supplements on your doctor's advice.
- Instead of using pills, vitamin E should be obtained from food. Whole grains, green leafy vegetables, seeds, nuts, and almonds are all healthy food sources of antioxidant as vitamin E. The RDA for vitamin E is 15mg per day (Barnard et al., 2014b).
- A patient's daily diet should include a dependable source of vitamin B12, such as supplements or fortified foods that supply at least the necessary daily dietary quantity (for adults 2.4 mg per day). Regularly check your vitamin B12 levels because a number of factors, including aging, may impair absorption.
- Even though research on aluminum's connection to Alzheimer's disease is ongoing, those who want to limit their exposure can stay away from baking powder, antacids, aluminum cookware, and other goods.
- Include aerobic exercise in patients' daily activities, which is the equivalent of 40 minutes of brisk walking three times each week (Barnard et al., 2014b).

In addition to the aforementioned recommendations, other actions need more research in order to be considered for inclusion in next preventive guidelines.

These might include the advice listed below:

- You should adhere to a sleep regimen that will ensure you receive adequate sleep each night, which for most individuals is 7-8 hours. Obstructive sleep apnea, for example, should be evaluated and treated if there are any underlying sleep problems. Sleep issues have been related with cognitive decline in elderly people.
- Engage in regular mental activities to promote learning new things, such as spending 30 minutes a day, four to five times per week. More mentally active people are less likely to develop cognitive issues later in life, according to a variety of studies (Galvin,2017).

The development of Alzheimer's disease can be postponed by engaging in physical activity, mental stimulation, calorie restriction, and social interactions. Cohort studies suggest that aerobic exercise and other forms of physical activity can aid with AD deficits.

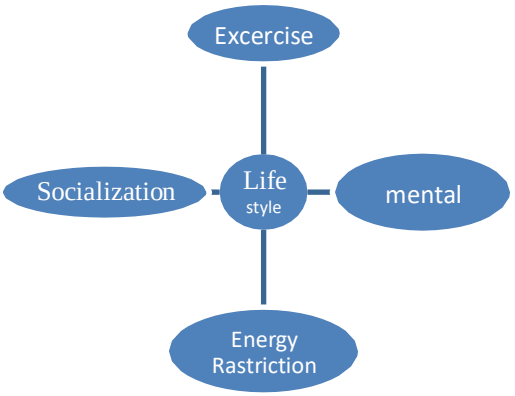

Figure 5:Nonpharmacologicaltreatments (Mendiola-Precoma et al., 2016)

The outcomes showed enhanced cognition in the water maze test as well as lower levels of amyloid-β and inflammation. Lack of socialization has been linked to several disorders, including depression, alcoholism, obesity, diabetes, hypertension, Alzheimer's disease, and cancer. Socialization is crucial for the mental and physical development of humans.

Chapter 4

Discussion

Nowadays nutritional supplements are used to treat Alzheimer's disease because there is no established pharmacological medicine available for this treatment. However, Available pharmacological drug such as cholinesterase inhibitor, glutamate antagonist is used to minimize symptoms or slow down damage progression but this are not able to cure the disease. Besides, some etiology based treatments like amyloid binder, anti-Aβ aggregation compounds, tau therapies are still under clinical trials. On the other hand, when nutritional supplements are given to the patients with AD, good improvements developed on them. When people consumed a supplement or combination formula, some research found that participants' cognitive function either improved or at least slowed down. On the other hand, the majority of epidemiological investigations revealed a weak or inconsistent link between taking a mix of multivitamin supplements and an improvement in cognition. Selenium, fiber, iron, and vitamins B, C, K, and E deficiencies were common in AD patients. Not just α-tocopherol-rich diets but also those high in other forms of vitamin E had beneficial effects. Interventional research on omega-3 or vitamin B supplements revealed minimal real mental advancements.

Chapter 5

Conclusion

According to epidemiological research, some nutrients, including PUFAs, vitamins, minerals, prebiotics, probiotics, symbiotic compounds, polyphenols, antioxidants, and strategically planned dietary components, might influence the risk of cognitive decline and halt the onset of AD. Nutritional status changes with aging have a significant impact on how well the brain functions. Elderly people's susceptibility to certain food deficits may make damaged brain processes worse. Both the general public and the scientific community are very interested in the possibility of dietary supplements to delay cognitive decline by preventing harmful neurodegenerative and pathogenic processes. According to current research, the most effective therapeutic approach may involve a multi-nutritional (rather than a single nutrient) intervention that targets several disease-related factors, including Aβ, synaptic loss,

neurofibrillary tangles, the vascular system, inflammation, and oxidative stress. Pharmacological treatments such as acetylcholinesterase inhibitors, N-methyl-D-aspertate receptor antagonists, secretase inhibitors, Amyloid binders, Anti-Aβ Aggregation compounds, Tau therapies, and other neurotransmitter systems are currently used to manage AD. There is no justification for supplementing nutrients above physiological levels, especially considering the synergy between nutrients that has been seen in several kinds of research. From a safety standpoint, nutritional supplements could be given to AD patients who are already on anti-AD medication as an add-on therapy. People who are at risk for AD may experience pathological alterations in their brains 20 to 30 years prior to the onset of clinical dementia symptoms. Therefore, there is a larger chance of preventing or delaying cognitive decline and AD the earlier nutritional supplementation can be started. When damage is limited, preserving neural tissue, cells, and synapses may provide the most significant long-term results. The development of earlier neurodegenerative process identification is required, particularly in people who are more at risk of developing AD. However, supplementing with particular nutrients that support the brain may still be able to prevent further decline or perhaps improve brain function even if the disease is far along in the progress.

References

Abate, G., Marziano, M., Rungratanawanich, W., Memo, M., & Uberti, D. (2017). Nutrition and AGE-ing: Focusing on Alzheimer's Disease. In Oxidative Medicine and Cellular Longevity (Vol. 2017). https://doi.org/10.1155/2017/703981

Ayton, S., Lei, P., & Bush, A. I. (2013). Metallostasis in Alzheimer's disease. In Free Radical Biology and Medicine (Vol. 62, pp. 76–89). Elsevier Inc. https://doi.org/10.1016/j.freeradbiomed.2012.10.558

Ak Pivi, G., Da Silva, R. V, Juliano, Y., Novo, N. F., Okamoto, I. H., Brant, C. Q., & Bertolucci, P. H. (2011). A prospective study of nutrition education and oral nutritional supplementation in patients with Alzheimer's disease. http://www.nutritionj.com/content/10/1/98

Barnard, N. D., Bush, A. I., Ceccarelli, A., Cooper, J., de Jager, C. A., Erickson, K. I., Fraser, G., Kesler, S., Levin, S. M., Lucey, B., Morris, M. C., &Squitti, R. (2014). Dietary and lifestyle guidelines for the prevention of Alzheimer's disease. In *Neurobiology of Aging* (Vol. 35, Issue SUPPL2). Elsevier Inc. https://doi.org/10.1016/j.neurobiolaging.2014.03.033

Bell, I. R. (2005). Diet and Nutrition in Alzheimer's Disease and Other Dementias of Late Life. *Explore: The Journal of Science and Healing*, *1*(4). https://doi.org/10.1016/j.explore.2005.04.003

Bird, T. D. (2008). Genetic aspects of Alzheimer disease. In *Genetics in Medicine*

C. C., Siemers, E., Stern, Y., Yaffe, K., Carrillo, M. C., Thies, B., Morrison-Bogorad, M., … Phelps, C. H. (2011). Toward defining the preclinical stages of Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's and Dementia*, *7*(3), 280–292. https://doi.org/10.1016/j.jalz.2011.03.003

Cardoso, B. R., Ong, T. P., Jacob-Filho, W., Jaluul, O., Freitas, M. I. D. Á., & Cozzolino, S. M. F. (2010). Nutritional status of selenium in Alzheimer's disease patients. *British Journal of Nutrition*, *103*(6), 803–806. https://doi.org/10.1017/S0007114509992832

Castellani, R. J., Rolston, R. K., & Smith, M. A. (2010). Alzheimer disease. In *Disease-a-Month* (Vol. 56, Issue 9, pp. 484–546). Mosby Inc. https://doi.org/10.1016/j.disamonth.2010.06.001

Citron, M. (2004). Strategies for disease modification in Alzheimer's disease. In *Nature Reviews Neuroscience* (Vol. 5, Issue 9, pp. 677–685). https://doi.org/10.1038/nrn1495

Cooper, J. K. (2014). Nutrition and the brain: What advice should we give? In*Neurobiology of Aging* (Vol. 35, Issue SUPPL.2). https://doi.org/10.1016/j.neurobiolaging.2014.02.029

Cremonini, A. L., Caffa, I., Cea, M., Nencioni, A., Odetti, P., &Monacelli, F. (2019). Nutrients in the Prevention of Alzheimer's Disease. In *Oxidative Medicine and Cellular Longevity* (Vol. 2019). Hindawi Limited. https://doi.org/10.1155/2019/9874159

Crous-Bou, M., Minguillón, C., Gramunt, N., &Molinuevo, J. L. (2017). Alzheimer's disease prevention: From risk factors to early intervention. In *Alzheimer's Research and Therapy* (Vol. 9, Issue 1). BioMed Central Ltd. https://doi.org/10.1186/s13195- 017-0297-z

Cummings, J. L., & Cole, G. (n.d.). *Alzheimer Disease*. http://jama.jamanetwork.com/

Dangour, A. D., Whitehouse, P. J., Rafferty, K., Mitchell, S. A., Smith, L., Hawkesworth, S., &Vellas, B. (2010). B-vitamins and fatty acids in the prevention and treatment of Alzheimer's disease and dementia: A systematic review. In *Journal of Alzheimer's Disease* (Vol. 22, Issue 1). https://doi.org/10.3233/JAD-2010-090940

de Wilde, M. C., Vellas, B., Girault, E., Yavuz, A. C., &Sijben, J. W. (2017). Lower brain and blood nutrient status in Alzhiemer's disease: Results from meta-analyses. In *Alzheimer's and Dementia: Translational Research and Clinical Interventions* (Vol.3, Issue 3, pp. 416–431). Elsevier Inc. https://doi.org/10.1016/j.trci.2017.06.002

dementia. *Journal of Internal Medicine*, *275*(3), 229–250. https://doi.org/10.1111/joim.12178

Deture, M. A., & Dickson, D. W. (2019). The neuropathological diagnosis of Alzheimer's disease. In *Molecular Neurodegeneration* (Vol. 14, Issue 1). https://doi.org/

Doraiswamy, P. M., &Xiong, G. L. (2006). Pharmacological strategies for the prevention of Alzheimer's disease. In *Expert Opinion on Pharmacotherapy* (Vol. 7, Issue 1, pp. 1–10). https://doi.org/10.1517/14656566.7.1.1

Du, X., Wang, C., & Liu, Q. (2015). Potential Roles of Selenium and Selenoproteins in the Prevention of Alzheimer';s Disease. *Current Topics in Medicinal Chemistry*, *16*(8). https://doi.org/10.2174/1568026615666150827094936

Dziuba, S., Cierniak-Emerych, A., Klímová, B., Poulová, P., Napora, P., & Szromba,

Edwards, N. E., & Beck, A. M. (2002). Animal-Assisted Therapy and Nutrition in Alzheimer's Disease 1. *Western Journal of Nursing Research*, *24*(6). https://doi.org/10.1177/019394502236642

Fox, P. (n.d.). *From Senility to Alzheimer's Disease: The Rise of the Alzheimer's Disease Movement*.

Galvin, J. E. (2017). Prevention of Alzheimer's Disease: Lessons Learned and Applied. *Journal of the American Geriatrics Society*, *65*(10), 2128–2133. https://doi.org/10.1111/jgs.14997

George, D. R., Dangour, A. D., Smith, L., Ruddick, J., Vellas, B., & Whitehouse, P. J. (2009). The role of nutrients in the prevention and treatment of Alzheimer's disease:

Goedert, M., &Spillantini, M. G. (2006). A century of Alzheimer's disease. In *Science*

Graham, W. V., Bonito-Oliva, A., &Sakmar, T. P. (2017). Update on Alzheimer's

Disease Therapy and Prevention Strategies. In *Annual Review of Medicine* (Vol. 68, pp. 413–430). Annual Reviews Inc. https://doi.org/10.1146/annurev-med-042915-103753

Grant, W. B. (2014). Trends in diet and Alzheimer's disease during the nutrition transition in Japan and developing countries. *Journal of Alzheimer's Disease*, *38*(3). https://doi.org/10.3233/JAD-130719

Hardy, J. (2006). A Hundred Years of Alzheimer's Disease Research. In *Neuron* (Vol. 52, Issue 1, pp. 3–13). https://doi.org/10.1016/j.neuron.2006.09.016

Heneka, M. T., O'Banion, M. K., Terwel, D., &Kummer, M. P. (2010). Neuroinflammatory processes in Alzheimer's disease. In *Journal of Neural Transmission* (Vol. 117, Issue 8, pp. 919–947). https://doi.org/10.1007/s00702-010-0438-z

Hu, N., Yu, J. T., Tan, L., Wang, Y. L., Sun, L., & Tan, L. (2013). Nutrition and the risk of alzheimer's disease. In *BioMed Research International* (Vol. 2013). https://doi.org/10.1155/2013/524820

Hyman, B. T., Phelps, C. H., Beach, T. G., Bigio, E. H., Cairns, N. J., Carrillo, M. C., Dickson, D. W., Duyckaerts, C., Frosch, M. P., Masliah, E., Mirra, S. S., Nelson, P. T., Schneider, J. A., Thal, D. R., Thies, B., Trojanowski, J. Q., Vinters, H. V., &Montine, T. J. (2012). National Institute on Aging-Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease. *Alzheimer's and Dementia*, *8*(1), 1–13. https://doi.org/10.1016/j.jalz.2011.10.007

Imtiaz, B., Tolppanen, A. M., Kivipelto, M., &Soininen, H. (2014). Future directions in Alzheimer's disease from risk factors to prevention. In *Biochemical Pharmacology* (Vol. 88, Issue 4, pp. 661–670). Elsevier Inc. https://doi.org/10.1016/j.bcp.2014.01.003

J. Dominguez, L., &Barbagallo, M. (2016). Dietary Approaches and Supplements in the Prevention of Cognitive Decline and Alzheimer';s Disease. *Current Pharmaceutical Design*, *22*(6). https://doi.org/10.2174/1381612822666151204000733

Jackson, J. M., Bay, A. A., Barter, J. D., Ni, L., Caudle, W. M., Serra, M. C., Wharton, W., & Hackney, M. E. (2020). The Role of Nutrition and Inflammation on Cognition in a High-Risk Group for Alzheimer's Disease. *Journal of Alzheimer's Disease Reports*, *4*(1). https://doi.org/10.3233/adr-200224

Jellinger, K. A. (2006). Alzheimer 100 - Highlights in the history of Alzheimer research. In *Journal of Neural Transmission* (Vol. 113, Issue 11). https://doi.org/10.1007/s00702-006-0578-3

Kamphuis, P. J., &Wurtman, R. J. (n.d.). *Nutrition and AlzheimerÕs disease: pre- clinical concepts*.

Kigozi, E., Egwela, C., Kamoga, L., Mbalinda, S. N., &Kaddumukasa, M. (2021). Nutrition challenges of patients with alzheimer's disease and related dementias: A qualitative study from the perspective of caretakers in a mental national referral hospital. *Neuropsychiatric Disease and Treatment*, *17*. https://doi.org/10.2147/NDT.S325463

Liu, J., & Ames, B. N. (2005). Reducing mitochondrial decay with mitochondrial nutrients to delay and treat cognitive dysfunction, Alzheimer's disease, and Parkinson's disease. In *Nutritional Neuroscience* (Vol. 8, Issue 2, pp. 67–89). https://doi.org/10.1080/10284150500047161

Lopes Da Silva, S., Vellas, B., Elemans, S., Luchsinger, J., Kamphuis, P., Yaffe, K., Sijben, J., Groenendijk, M., &Stijnen, T. (2014). Plasma nutrient status of patients with Alzheimer's disease: Systematic review and meta-analysis. In *Alzheimer's and Dementia* (Vol. 10, Issue 4, pp. 485–502). Elsevier Inc.

https://doi.org/10.1016/j.jalz.2013.05.1771

Lots of people are forgetful. Are there any particular warning signs of Alzheimer's disease? (2009). www.alzforum.org

Martins, L. B., Malheiros Silveira, A. L., & Teixeira, A. L. (2021). The link between nutrition and Alzheimer's disease: From prevention to treatment. In *Neurodegenerative Disease Management* (Vol. 11, Issue 2). https://doi.org/10.2217/nmt-2020-0023

Mattson, M. P. (2004). *Pathways towards and away from Alzheimer's disease*. www.nature.com/nature

Mayeux, R. (2010). Early Alzheimer's Disease. *New England Journal of Medicine*, *362*(23), 2194–2201. https://doi.org/10.1056/nejmcp0910236

Methodology for a systematic review. In *European Journal of Neurology* (Vol. 16, Issue SUPPL. 1). https://doi.org/10.1111/j.1468-1331.2009.02736.x

Mi, W., van Wijk, N., Cansev, M., Sijben, J. W. C., &Kamphuis, P. J. G. H. (2013). Nutritional approaches in the risk reduction and management of Alzheimer's disease. In *Nutrition* (Vol. 29, Issue 9, pp. 1080–1089). https://doi.org/10.1016/j.nut.2013.01.024

Miranda, A., Gómez-Gaete, C., &Mennickent, S. (2017). [Role of Mediterranean diet on the prevention of Alzheimer disease]. *Revista Medica de Chile*, *145*(4). https://doi.org/10.4067/S0034-98872017000400010

Morris, M. C. (n.d.). *The role of nutrition in AlzheimerÕs disease: epidemiological evidence*.

Mosconi, L., & McHugh, P. F. (2015). Let Food Be Thy Medicine: Diet, Nutrition, and Biomarkers' Risk of Alzheimer's Disease. In *Current Nutrition Reports* (Vol. 4, Issue 2). https://doi.org/10.1007/s13668-014-0111-5

Naderali, E. K., Ratcliffe, S. H., & Dale, M. C. (2009). Obesity and alzheimer?s disease: A link between body weight and cognitive function in old age. In *American Journal of Alzheimer's Disease and other Dementias* (Vol. 24, Issue 6). https://doi.org/10.1177/1533317509348208

Norton, S., Matthews, F. E., Barnes, D. E., Yaffe, K., &Brayne, C. (2014). Potential for primary prevention of Alzheimer's disease: An analysis of population-based data. *The Lancet Neurology*, *13*(8), 788–794. https://doi.org/10.1016/S1474-4422(14)70136-X

Norwitz, N. G., Saif, N., Ariza, I. E., & Isaacson, R. S. (2021). Precision nutrition for alzheimer's prevention in apoe4 carriers. *Nutrients*, *13*(4). https://doi.org/10.3390/nu13041362

Otaegui-Arrazola, A., Amiano, P., Elbusto, A., Urdaneta, E., & Martínez-Lage, P. (2014). Diet, cognition, and Alzheimer's disease: Food for thought. In *European Journal of Nutrition* (Vol. 53, Issue 1, pp. 1–23). https://doi.org/10.1007/s00394-013- 0561-3

P. H. F. (2017). Nutritional management for Alzheimer's disease in all stages: mild, moderate, and severe. In *Nutrire* (Vol. 42, Issue 1). https://doi.org/10.1186/s41110-016-0025-7

Perez-Cruz, C., & Díaz-Cintra, S. (2015). Editorial: Nutrition and prevention of Alzheimer's disease. In *Frontiers in Aging Neuroscience* (Vol. 7, Issue SEP). https://doi.org/10.3389/fnagi.2015.00170

Pivi, G. A. K., Da Silva, R. V., Juliano, Y., Novo, N. F., Okamoto, I. H., Brant, C. Q., & Bertolucci, P. H. F. (2011). A prospective study of nutrition education and oral nutritional supplementation in patients with Alzheimer's disease. *Nutrition Journal*, *10*(1). https://doi.org/10.1186/1475-2891-10-98

Polidori, M. C. (2014). Preventive benefits of natural nutrition and lifestyle counseling against alzheimer's disease onset. In *Journal of Alzheimer's Disease* (Vol. 42). https://doi.org/10.3233/JAD-141539

Power, R., Prado-Cabrero, A., Mulcahy, R., Howard, A., & Nolan, J. M. (2019). The Role of Nutrition for the Aging Population: Implications for Cognition and Alzheimer's Disease. In *Annual Review of Food Science and Technology* (Vol. 10). https://doi.org/10.1146/annurev-food-030216-030125

Rajna, Z., Mattila, H., Huotari, N., Tuovinen, T., Krüger, J., Holst, S. C., Korhonen, V., Remes, A. M., Seppänen, T., Hennig, J., Nedergaard, M., &Kiviniemi, V. (2021). Cardiovascular brain impulses in Alzheimer's disease. *Brain*, *144*(7). https://doi.org/10.1093/brain/awab14

Ravi, S. K., Narasingappa, R. B., & Vincent, B. (2019). Neuro-nutrients as anti- alzheimer's disease agents: A critical review. In *Critical Reviews in Food Science and Nutrition* (Vol. 59, Issue 18, pp. 2999–3018). Taylor and Francis Inc. https://doi.org/10.1080/10408398.2018.1481012

Risk, D. (2021). *What Do We Know About Diet and Prevention of Alzheimer ' s Disease?* National Institute on Aging.

Rolland, Y., Abellan van Kan, G., &Vellas, B. (2008). Physical Activity and Alzheimer's Disease: From Prevention to Therapeutic Perspectives. In *Journal of the American Medical Directors Association* (Vol. 9, Issue 6, pp. 390–405). Elsevier Inc. https://doi.org/10.1016/j.jamda.2008.02.007

Romanenko, M., Kholin, V., Koliada, A., &Vaiserman, A. (2021). Nutrition, Gut Microbiota, and Alzheimer's Disease. In *Frontiers in Psychiatry* (Vol. 12). https://doi.org/10.3389/fpsyt.2021.712673

S. (2020). Organic foods in diets of patients with Alzheimer's disease. *Sustainability (Switzerland)*, *12*(4). https://doi.org/10.3390/su12041388

Sandman, P. -O, Adolfsson, R., Nygren, C., Hallmans, G., &Winblad, B. (1987). Nutritional Status and Dietary Intake in Institutionalized Patients With Alzheimer's Disease and

Multiinfarct Dementia. *Journal of the American Geriatrics Society*, *35*(1), 31–38. https://doi.org/10.1111/j.1532-5415.1987.tb01316.

Seneff, S., Wainwright, G., &Mascitelli, L. (2011). Nutrition and Alzheimer's disease: The detrimental role of a high carbohydrate diet. In *European Journal of Internal Medicine* (Vol. 22, Issue 2, pp. 134–140). Elsevier B.V. https://doi.org/10.1016/j.ejim.2010.12.017

Serrano-Pozo, A., Frosch, M. P., Masliah, E., & Hyman, B. T. (2011). Neuropathological alterations in Alzheimer disease. *Cold Spring Harbor Perspectives in Medicine*, *1*(1). https://doi.org/10.1101/cshperspect.a006189

Shah, R. (2013). The role of nutrition and diet in Alzheimer disease: A systematic review. In *Journal of the American Medical Directors Association* (Vol. 14, Issue 6, pp. 398–402). Elsevier Inc. https://doi.org/10.1016/j.jamda.2013.01.014

Sharma, P., Gaur, V. K., & Srivastava, J. K. (2019). Diet and nutrition in alzheimer's disease and healthy aging. In *Biological, Diagnostic and Therapeutic Advances in Alzheimer's Disease: Non-Pharmacological Therapies for Alzheimer's Disease*. https://doi.org/10.1007/978-981-13-9636-6_10

Shea, T. B., & Remington, R. (2015). Nutritional supplementation for Alzheimer's disease? In *Current Opinion in Psychiatry* (Vol. 28, Issue 2). https://doi.org/10.1097/YCO.0000000000000138

Śliwińska, S., &Jeziorek, M. (2021). The role of nutrition in Alzheimer's disease. *RocznikiPanstwowegoZakladuHigieny*,*72*(1).https://doi.org/10.32394/rpzh.2021.0154

Smith, M. A. (1998). *ALZHEIMER DISEASE*.

Solomon, A., Mangialasche, F., Richard, E., Andrieu, S., Bennett, D. A., Breteler, M., Fratiglioni, L., Hooshmand, B., Khachaturian, A. S., Schneider, L. S., Skoog, I., &Kivipelto, M. (2014). Advances in the prevention of Alzheimer's disease and dementia. *Journal of Internal Medicine*, *275*(3), 229–250.

https://doi.org/10.1111/joim.12178

Sperling, R. A., Aisen, P. S., Beckett, L. A., Bennett, D. A., Craft, S., Fagan, A. M., Iwatsubo, T., Jack, C. R., Kaye, J., Montine, T. J., Park, D. C., Reiman, E. M., Rowe,

Steele, M., Stuchbury, G., &Münch, G. (2007). The molecular basis of the prevention of Alzheimer's disease through healthy nutrition. *Experimental Gerontology*, *42*(1–2). https://doi.org/10.1016/j.exger.2006.06.002

Tanzi, R. E. (2012). The genetics of Alzheimer disease. *Cold Spring Harbor Perspectives in Medicine*, *2*(10). https://doi.org/10.1101/cshperspect.a006296

van der Beek, E. M., &Kamphuis, P. J. G. H. (2008). The potential role of nutritional components in the management of Alzheimer's Disease. In *European Journal of Pharmacology* (Vol. 585, Issue 1, pp. 197–207). https://doi.org/10.1016/j.ejphar.2008.01.049

Van Wijk, N., Broersen, L. M., De Wilde, M. C., Hageman, R. J. J., Groenendijk, M., Sijben, J. W. C., &Kamphuis, P. J. G. H. (2014). Targeting synaptic dysfunction in Alzheimer's disease by administering a specific nutrient combination. In *Journal of Alzheimer's Disease* (Vol. 38, Issue 3, pp. 459–479). IOS Press. https://doi.org/10.3233/JAD-130998

Venturini, L., Perna, S., Sardi, F., Faliva, M. A., Cavagna, P., Bernardinelli, L.,Ricevuti, G., &Rondanelli, M. (2014). Alzheimer's Disease: From Genes to Nutrition. *European Journal of Inflammation*, *12*(3). https://doi.org/10.1177/1721727x1401200301

von Arnim, C. A. F., Gola, U., &Biesalski, H. K. (2010). More than the sum of its parts? Nutrition in Alzheimer's disease. In *Nutrition* (Vol. 26, Issues 7–8, pp. 694– 700). https://doi.org/10.1016/j.nut.2009.11.009

Wisniewski, T., &Goñi, F. (2015). Immunotherapeutic Approaches for Alzheimer's Disease. In *Neuron* (Vol. 85, Issue 6, pp. 1162–1176). Cell Press. https://doi.org/10.1016/j.neuron.2014.12.064

Ye, J., &Zhai, H. Z. (2005). Oxidative stress and Alzheimer disease. Chinese Journal of Clinical Rehabilitation, 9(33), 117–119.

Young, K. W. H., Greenwood, C. E., Robert Van Reekum, Ã., &Binns, M. A. (2004). Providing Nutrition Supplements to Institutionalized Seniors with Probable Alzheimer's Disease Is Least Beneficial to Those with Low Body Weight Status. In *J Am Geriatr Soc* (Vol. 52).

Zhang, X. X., Tian, Y., Wang, Z. T., Ma, Y. H., Tan, L., & Yu, J. T. (2021). The Epidemiology of Alzheimer's Disease Modifiable Risk Factors and Prevention. In *Journal of Prevention of Alzheimer's Disease* (Vol. 8, Issue 3). https://doi.org/10.14283/jpad.20