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DIPLOMA THESIS (DT)

**NUTRITIONAL FACTORS
IN ETIOPATHOGENESIS OF
ALZHEIMER'S DISEASE**

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2. ABSTRACT

Alzheimer's disease (AD) is a genetic, progressive, neurodegenerative disorder. AD is responsible for the vast majority of dementia cases, and the increasing prevalence of the disease worldwide is a major public health concern.

This paper provides evidence from epidemiological studies is mounting that diet and nutrition are among the many potential risk factors being investigated in relation to the development of AD. These factors are closely related to our way of life, what we eat, and the pathophysiology that can modify and prevent in our day-to-day activities.

Since there currently exists no effective and proven treatment or preventative measure for AD, increasing focus is being placed on disease prevention in general and the healthy diet in particular. To reduce the probability of developing AD, preventive intervention should be started as early as possible.

Due to the neurodegenerative characteristics of this condition, adequate diet must be taken into account as it has both protective and preventative benefits. These include caffeine, isoflavone phytoestrogen, polyphenols, vitamin B, vitamin D, antioxidant vitamins (vitamins C, E, beta-carotene), minerals (avoid copper, iron, and aluminium), unsaturated fatty acids, vitamin B, and vitamin D.

There is evidence that the DASH, Mediterranean, and ketogenic diets can prevent and delay AD. A Mediterranean diet, on the other hand, may have a protective impact on the neurodegenerative process considering that it is rich in antioxidants, fibre, and omega-3 polyunsaturated fatty acids. The MIND diet, which combines the both Mediterranean and DASH diets, has been shown to be far more powerful than either diet alone in reducing cognitive decline and dementia.

3. INTRODUCTION

Alzheimer's disease (AD), a degenerative cognitive condition that profoundly affects brain pathophysiology and hasn't been a proven cure yet, is one of the most frequent causes of dementia. The prognosis of memory, judgment and social abilities might be moderately attenuated and impaired by this common chronic and irreversible brain illness. AD is characterised by forming extracellular senile plaques composed of beta-amyloid peptide and tau protein, as well as intracellular neurofibrillary tangles (Winslow BT. et al., 2014). The combination of these two defining characteristics is fatal, resulting in brain dysfunction and neuronal death (Ising C. et al., 2015). Other indications of AD, including synapse loss, oxidative stress, significant hippocampal and cortical gliosis, and a build-up of vascular amyloid plaques in the brain, all add to the disease's characteristic impairment of neurological function (Winslow BT. et al., 2014). Additionally, there is a reduction in cerebral volume and neuroinflammation. Although the cause of AD is unknown, its progression can be affected by numerous genetic and environmental factors, including dietary habits (Fernández-Sanz P. et al., 2019).

Memory loss is one the most common symptom of AD in the milder early stage due to its neurodegenerative pathogenesis in the brain. Throughout the terminal stages of the disorder, the patient is entirely reliant on others, having difficulties with driving and showering. To check patient's pathogenesis and symptom are an essential by using clinical dementia rating to determine and guide on the management of the AD.

Due to the irreversible fact of this disease, there are only a few pharmaceutical treatments and therapies that are available that could be able to delay the progression of AD (not 100% cure), including medication, diet, oestrogen, nutrients, and physical exercise (Winslow BT. et al., 2014). There are only four available evidence-based medications by a block of an acetylcholinesterase inhibitor and/or glutamate action. In the new study, cell and gene therapy strategies can be used (Yiannopoulou KG. et al., 2020). The most often utilised stem cell types in AD research now are induced pluripotent stem cells (iPSCs), mesenchymal stem cells (MSCs), brain-derived neural stem cells (NSCs), and embryonic stem cells (ESCs) (Liu XY. et al., 2020). Additionally, cholinergic neurons, mitochondria, and mitophagy are dysfunctional in AD neurons. Since mitophagy plays a role in the onset and progression of neurodegenerative diseases,

researchers are considering a wide range of preclinical treatment approaches (Cai Q. et al., 2020). According to Winslow BT. et al., 2014, has been demonstrated that oestrogen showed ineffective activity on the AD for both prevention and treatment, in the single use of the oestrogen. However some studies believe, oestrogen may protect the brain against AD by preventing inflammatory damage to cholinergic neurons and improving the functional status of cholinergic projections to the hippocampus and cortex, which can minimise the severity of AD in postmenopausal women, according to a study that supports the use of oestrogen replacement therapy (Cholerton B. et al., 2002; Vinogradova Y. et al., 2021).

According to recent research, diet may play a role in AD such as Antioxidants, fish, polyphenols, and vitamins have all been shown to reduce the risk of AD, whereas excessive consumption of calories, saturated fats, and alcohol increases the risk (Gardener SL. et al., 2018). In order to study the linkage between nutrition and AD, dietary patterns have recently arisen that more appropriately represent the complexity of food. The data connecting diet and lifestyle factors to AD risk and etiopathogenesis is examined in this review.

As AD develops, it is additionally associated with nutrition, the risk of losing weight, and a deteriorating nutritional state. Both excessive weight loss and hunger are risk factors for cognitive decline, which can result in the need for institutional care or even death (Marino LV. et al., 2015). Several minerals, micronutrients, and vitamins have protective properties against oxidative stress, neuroinflammation, and cognitive decline. Antioxidants, anti-inflammatory agents, and free radical scavengers are some of these properties (Mielech A. et al., 2020). Dopaminergic, serotonergic, and adrenergic neurotransmission are all impaired as a result of the cerebral cortex damage caused by AD. These neurotransmitters regulate eating behaviour; consequently, a gradual loss of appetite followed by a cessation of ingestion leads to a substantial decrease in the number of nutrients taken into the body (Prucoli J. et al., 2021).

Exercise and cognitive activity can lower AD risk, although APOE 4, diabetes, smoking, and depression can raise the risk. Genetic factors can cause AD, such as APOE 4, which is the risk gene involved in the lipid transport metabolism.

4. AIM OF THE DIPLOMA THESIS

The main goal of AD is to improve the quality-of-life span and delay the progression of pathogenesis. Thus, the purpose of this DT is to shed light on this concern by helping in understating the causes and risk factors of AD and give a concept of prophylactic concerns that are commonly encountered in our life to decrease the risk of irreversible disease, AD.

The data connecting protective and risk factors of AD and etiopathogenesis is examined in this review.

5. LIFESTYLE RISK FACTORS OF AD

5.1 Physical exercise

The size of the Hippocampal is closely related to physical exercise, which can increase or decrease the density. Yearly hippocampus density atrophy in older people with cognitively normal brains is between 1 and 2 per cent. Those who are physically inactive as people age experience a decline in mental ability and get a high chance of developing AD. Which is the known modifiable risk factor that physical activity may be beneficial to the brain because it protects against cognitive decline and preserves brain plasticity (Erickson KI. et al., 2011) by stopping or reversing hippocampal shrinkage and lowering amyloid deposition, which is an aid for disease's progression. The benefits of physical activity as a prophylactic measure by improving memory and cognitive function may also be identified through research on people individuals with dementia, mild cognitive impairment, and advanced age (Ebrahimi K. et al., 2017).

In a new investigation, a year of aerobic exercise increased the size of the hippocampus by 2% through increased cell proliferation, reversing the rapid age-related decline (Erickson KI. et al., 2011). The proliferation of neural stem cells and neurite development, both of which boost neurogenesis, occur in the dentate gyrus of the hippocampus, which is a critical part of learning and memory. Active seniors are characterised by bigger brains and greater executive function than sedentary seniors (Tseng BY. et al., 2013). Further, a year of moderate exercise alleviates its symptoms that slow the progression of activities of daily living and physical impairment in people with Alzheimer's disease (Pitkälä KH. et al., 2013).

Animal studies also provided proof that exercise is advantageous. To discover a positive correlation between inflammation and neuronal cell death in the hippocampus of intracerebroventricular and physical exercise, streptozotocin was injected into AD rats. Streptozotocin-treated mice did treadmill exercise for 30 minutes per day for 30 days. This clinical evidence carried out that the hippocampi of treated rats maintained cognitive function. While tauopathy, amyloidogenesis, neuroinflammation, and oxidative stress were reduced (Lu Y. et al., 2017). Similarly, the levels of total tau, ptau, and insoluble tau were reduced in the case of tau transgenic rats that were placed on a

treadmill for a period of time. However, this reduction was not connected to any neuroprotective advantages. The beneficial impact was also carried out in transgenic AD mice, which elevated c-Fos in the brain, evidence of a neuronal process that occurs after depolarisation which enhances the mice's spatial memory. In the case of healthy rats, the exercise demonstrated lower levels of beta-secretase (BACE) activity and amyloid precursor proteins (APP). BACE is a beta-site amyloid precursor protein cleaving enzyme which initiates toxic amyloid production that plays AD pathogenesis.

In Alzheimer's disease models, treadmill exercise increases Brain-derived Neurotrophic factor (BDNF) and TrkB (BDNF receptor) levels, stimulating cell proliferation and improving cognition. Borba et al. found a correlation between BDNF serum changes and hippocampus volume in mild cognitive impairment (MCI). BDNF plays a crucial role in forming long-term memories by promoting neurogenesis and dendritic growth. Raised level of BDNF, which in turn activates secretase and decreases amyloid peptides, both of which are amyloid precursor protein (APP) by-products. After intense exercise, adult hippocampus neurogenesis and BDNF levels must be stimulated in addition to exercise for cognitive benefits, compared to the resting level, according to new evidence

Working out activates the irisin. Irisin is a hormone which is exercise-related myokine that improves learning and memory function by regulating BDNF. AD mice showed both Long-term poor potentiation (LTP) and memory. Generally, Irisin levels are low in AD brains, making this myokine an intermediary of the preventative or ameliorative effects of exercise on AD pathology. This can reduce the toxicity of amyloid oligomers in vitro due to FNDC5/capacity irisin's to inhibit their binding to neurons (Edwards GA Iii et al., 2019).

5.2 Insomnia

In a 24-hour period, there are 16 hours of wakefulness and 8 hours of sleep. This pattern, which is governed by the circadian rhythm and sleep balance, is essential for various brain processes and the elimination of daytime toxins. Rapid Eye Movement (REM) sleep follows each stage of non-rapid eye movement sleep (NREM) has 3threestages: N1, N2, and N3). REM sleep is the most important phase of the sleep-wake cycle because the brain undergoes rewiring. With age, both REM sleep and total nightly sleep duration

decrease. AD patients commonly exhibit amplified daytime sleep, decreased night-time sleep, and sleep fragmentation. AD patients' electroencephalograms reveal an increase in N1 and N2 of NREM sleep, as well as REM latency, and a decrease in REM sleep, which ultimately shortens the total amount of time spent sleeping. Recent research suggests that NREM characteristics may foretell cognitive decline and that extended sleep duration may indicate a group at risk. Due to the correlation between ageing cognitive decline, and sleep problems, sleep disturbances may add to the risk of AD.

Sleep deprivation has been linked to mild cognitive weakening as well as dementia (Lim MM. et al., 2014). Beta-amyloid deposition appears to diminish the efficacy of sleep, particularly in the preclinical phases (López-García S. et al., 2021).

Constant exposure to light decreases sleep, which inhibits the sleep-wake cycle hormone melatonin, and exacerbates memory impairment and insoluble tau accumulation. Melatonin regulate important kinase such as glycogen synthase kinase 3 beta and cyclin-dependent kinase 5 which decrease hyperphosphorylation of tau (Shukla M. et al., 2017)

In sleep-deprived individuals, tau levels in the cerebrospinal fluid (CSF) rose by approximately 50 per cent. Prior to the onset of cognitive problems, a disruption in the normal sleep-wake cycle is one of the first signs of AD. Consequently, it is possible that alterations in the sleep-wake cycle are a risk factor for AD and that their early treatment can prevent or reduce the pathology and development of AD (López-García S. et al., 2021).

During sleep, the glymphatic system (macroscopic waste clearance system) is more effective at eliminating amyloid. In reality, the concentration of interstitial amyloid was higher in awake individuals than in those who were asleep, indicating that amyloid production is elevated during wakefulness. The glymphatic system uses water channels called astrocytic aquaporin 4 (AQP4) to facilitate the whole convective flow of interstitial fluid in order to remove waste (ISF). In the case of AD, having a lack of AQP4 channels leads to glymphatic system impairment that decreases neurodegenerative waste disposal (Reddy OC. et al., 2020; Silva I. et al., 2021).

Further, the interstitial space enlarges during sleep, facilitating CSF-ISF exchange and elimination, leading to beta-amyloid clearance. Direct involvement of sleep in the pathogenesis of AD has been shown by a complete night of acute sleep insomnia, which increases amyloid levels in the brain regardless of ApoE genotype. Tau levels in immature Schwann cells (ISC) decreased by 90% while sleeping (Holth JK. et al., 2019).

A lack of orexin, which is a neuropeptide that controls sleep and arousal, released during the day, has been shown to cause sleep disorders such as narcolepsy and muscle weakness conditions such as cataplexy. AD mice with elevated brain amyloid levels due to alertness or sleep restriction had their orexin receptors inhibited (Roh JH. et al., 2015).

5.3 Smoking

Tobacco use is responsible for the deaths of at least 6 million individuals per year. Neurocognitive issues are now frequently linked to cigarette smoking (World Health Organization, 2013). The well-documented cognitive effects of smoking include not only a decline in verbal memory but also a decrease in processing speed during visual search. There is a direct connection between the number of cigarettes smoked daily and the rate of mental decline. In addition, cardiovascular disorders are risk factors for AD, and the detrimental effects of smoking on these diseases highlight the role of smoking in causing dementia.

Many individuals believe that smoking can prevent AD because nicotine enhances short-term cognitive function and prevents amyloid formation. Due to the nicotine mechanism, that inhibits APP release, prevents aggregation, and lowers a burden in AD transgenic mice independent of inflammation. However, recent research has linked smoking to an elevated risk of cognitive damage and dementia. Nicotine worsens Tau phosphorylation in animal studies. Cigarette smoke worsens tau hyperphosphorylation and amyloid deposition, along with the inflammatory response, making it more indicative of AD. When epidemiological information is attuned to competing risks of death without AD, smoking does not appear to be linked to AD development (Abner EL. et al., 2018). Surprisingly, smokers who carry the ApoE4 allele, which is an AD risk gene, are protected from developing dementia (Edwards GA lii et al., 2019). To determine the precise

mechanism by which tobacco use may raise the risk of AD, additional research is required (Abner EL. et al., 2018).

5.4 Alcohol

Alcohol consumption is generally quite harmful to one's health. Men who consume four or more alcoholic beverages per day are considered heavy drinkers, as are women who consume three alcoholic beverages per day (Rehm J. et al., 2011). Heavy drinking is associated with a greater incidence of AD, but light to moderate drinking is associated with a lower risk (Heymann D. et al., 2016).

Heavy drinking promotes cognitive deterioration comparable to AD. Loss of cholinergic neurons in AD patients has also been documented in ethanol drinkers, along with hippocampus atrophy, associating excessive alcohol drinking with cognitive impairment that may promote AD. Doing both smoking and drinking can have a greater effect on the incidence of AD than either practice alone (Zhou S. et al., 2014). In the most recent research, alcohol consumption is not associated with either the onset or progression of AD (Bos I. et al., 2017). However, abstaining from alcohol after a diagnosis of AD appears to recover the cognitive deficits observed at diagnosis, indicating that heavy alcohol consumption increases the risk of AD and accelerates the disease's progression (Heymann D. et al., 2016). In addition, heavy drinking may result in an accumulation by impeding its elimination function via the glymphatic system, which is a link between alcohol and AD. The glymphatic system eliminates amyloid and other waste products from the brain. Thus, resulting in the cognitive impairments associated with alcohol consumption and AD.

Conversely, modest dosages of ethanol reduce A β -mediated synaptic dysfunction in AD animal models. Moderate wine intake (1-2 glasses per day) decreases the probability of amyloid deposit, mortality, and dementia, which may help to prevent AD. Thanks to the composition of the polyphenols, Tannins, Resveratrol, Quercetin, and Morin reduce oxidative stress, inflammation, and protein homeostasis, all of which contribute to controlling the formation of amyloid (Dhouafli Z. et al., 2018).

When assessing the effect of alcohol on AD dementia, it may be necessary to consider not only the frequency but also the duration, age, and type of alcoholic beverage (fermented versus distilled) (Bos I. et al., 2017).

6. DIETARY FACTOR – MICRO-&MACRONUTRIENTS

6.1 *Main macronutrients*

6.1.1 Dietary Fatty acids

Dietary intake and food preferences are considered to be key factors in the development of age-related neurodegenerative diseases in the elderly. A recent study of epidemiological data has connected dietary fatty acid considerations to AD, supporting the idea that additional central nervous system problems, as well as AD beginning and progression, are strongly affected by fatty acid metabolism (Zhang T. et al., 2020). Further, the amount and composition of body fat can lead to a greater risk of various diseases, including AD.

Diets high in saturated and trans fatty acids are connected to high cholesterol levels and unfavourable LDL: HDL ratios. The most prevalent cause of the risk of AD involves insulin resistance, dyslipidaemia, obesity, cardiovascular disease, diabetes, and metabolic disorder (Hildreth KL. et al., 2012). Palmitic acid, which is the most abundant saturated fatty acid, is significantly linked to all of these conditions (Dietschy JM., 1998).

New research, owing to the high intake of palmitic acids and saturated fatty acids boosting ceramide synthesis, which can lead to dyslipidaemia and insulin resistance, leading to significantly higher ceramide levels elevated in the brain tissue of AD patients (Mielke MM. et al., 2012; Reginato A. et al., 2021). Ceramides may have a significant role in the pathogenesis of AD, which participates in neuronal cell death (De La Monte SM., 2012). A greater risk of developing AD is linked to elevated basal serum levels of certain ceramide species. Additionally, it seems that serum ceramide levels differ depending on when memory loss first starts to occur. Ceramide levels are elevated in people with mild to moderate symptoms, which is significant because it illustrates that abnormalities in lipid metabolism show in the early phase of AD progression (Mielke MM. et al., 2012).

6.1.2 Trans-fatty acids

Our diet that contains trans-fat, commonly known as trans fatty acids, both occur naturally and chemically. Dietary trans fatty acids are included in many processed meals

and are naturally present in meat, milk, and other foodstuffs. Sweet pastries comprise the largest factor of elevated trans-fat content owing to margarine. A significant concentration of trans fat in the blood raises the chance of the onset of AD and other various matters such as cognitive decline, senescence, dyslipidaemia, diabetes, dementia, and cardiovascular disease.

The most prevalent trans fat found in processed foods is elaidic acid, which affects cholesterol levels by reducing the good cholesterol (HDL) and increasing LDL cholesterol. Researchers discovered that those with elevated blood levels of elaidic acid were 50 to 75 per cent more likely to acquire AD or another type of dementia than people with lower amounts of trans fatty acid (Honda T. et al., 2019)

Studies also suggested that high amounts of trans may decrease serotonin synthesis in the brain, leading to depression as well as adversely affecting memory and increasing inflammation in the brain.

Lastly, the incorporation of trans-fatty acids into membrane phospholipids alters membrane fluidity and the responses of numerous membrane receptors. As ligands for nuclear receptors, fatty acids can modulate metabolic and inflammatory responses directly (Khan SA. et al., 2003).

6.1.3 PUFA (Polyunsaturated fatty acids)

Unsaturated fatty acids compete with polyunsaturated fatty acid enzymes. Thromboxane, leukotrienes, and prostaglandins are all by-products of lipoxygenase and cyclo-oxygenase enzymes transforming PUFA.

Consuming large amounts of meat, which is abundant in n-6 PUFAs (linoleic acid, arachidonic acids), has been associated with an upregulation of inflammatory cytokines and eicosanoids, which produce signalling molecules susceptible to inflammation, atherogenesis, and thrombosis. The majority of PUFAs found in the central nervous system are docosahexaenoic acid (DHA), which is formed from linolenic acid.

DHA is an omega-3 fatty acid. In response to a diet high in DHA from fish and fish oil, the body produces eicosanoids, which have anti-thrombotic, anti-inflammatory, vasodilatory, and neuroprotective effects (Horrocks LA. et al., 2004). DHA and

arachidonic acids are PUFA which have a role in neurogenesis and development of the brain through the neuron membrane modulation through signal transduction with the G protein. Lipoproteins and Lysophospholipids in the bloodstream deliver arachidonic acids and DHA to the brain to help brain functioning. Due to their neuroprotective activity, these can decrease the pathogenesis of AD or other neurodegeneration diseases, which are also involved in neuroinflammation, oxidative stress, and mitochondrial dysfunction. Thus, the ratio of arachidonic acids to DHA in the diet may play a role in the development of nutrition-based disease prevention strategies. Despite the rarity of a deficiency in essential fatty acids, problems in converting linolenic acid to longer-chain PUFA may result from hormonal abnormalities, malnutrition, or both. Low linoleic acid due to poor dietary intake or abnormal metabolic processes indicates low DHA levels (Sambra V. et al., 2021).

The development of AD is fundamentally influenced by oxidative stress and mitochondrial dysfunction. (Kou J. et al., 2011). According to recent studies, AD patients had reduced peroxisomal D-bifunctional protein expression, increased THA levels, and impaired liver DHA synthesis. It has been proven that tetracosahexaenoic acid (THA) deposition has been shown to affect mitochondrial function. In the endoplasmic reticulum or microsomes, Eicosapentaenoic acid (EPA) is partially converted to DHA, but the conversion is completed in peroxisomes. Endoplasmic reticulum desaturation and two additional EPA elongation processes generate THA. THA is an extremely long-chain fatty acid that must undergo final oxidation in the peroxisome in order to produce DHA. This additional step may be responsible for the inefficient conversion of linolenic acid to DHA. (EPA → THA → DHA) (Astarita G. et al., 2010).

In addition, abnormal concentrations of the enzymes such as elongase and desaturase may contribute to a reduction in the production of longer-chain PUFA in AD. This may result in a loss of membrane fluidity together with an imbalance of signalling molecules derived from PUFAs, like docosanoids and eicosanoids (Bordoni A. et al., 1998). Because reduced long-chain PUFA transport to the brain may be linked with metabolic dysfunction and insulin resistance, these factors may contribute to the development of AD (Astarita G. et al., 2010).

6.1.4 Dietary Carbohydrates

Carbohydrates which contain in foods that increase blood glucose levels. In 1992, the USDA recommended adding no more than 40 grams of sugar to a 2000-calorie diet. Two types of carbs are existed such as complex and refined (simple) carbohydrates. A diet high in refined carbohydrate is highly involved in AD and metabolic syndrome that increase blood sugar level quickly, leading to insulin resistance (Brand-Miller JC., 2003), which shows a higher possibility of developing mild cognitive impairment leading to AD. Carbs in the diet AD risk factors, like cardiovascular disorder and type 2 diabetes, are affected by the quantity and composition of carbohydrates consumed.

High consumption of carbohydrates is involved in both fructose and insulin metabolism. Fructose is a monosaccharide which is formed via carbohydrate oxidation which initiates a survival mechanism to prevent animals from being hungry by reducing cell energy and causing adenosine monophosphate to break down into uric acid. Excessive fructose intake activates the overactivation of cerebral fructose metabolism, where fructose is mostly produced endogenously in the brain. Cerebral insulin resistance and mitochondrial dysfunction are the key factors to increasing the onset of AD, which involving in cerebral fructose metabolism. As a result, the insufficient neural glycolysis blocks the reduction in mitochondrial energy production, which leads to a gradual loss of cerebral energy levels necessary for neurons to continue functioning.

Insulin is a hormone that modulates glucose in the body, regulates sterol regulatory element-binding proteins (SREBPs) expression, which affects fatty acid and cholesterol production (Kok N. et al., 1996), besides acts as proteostasis, which block both beta-amyloid peptide and tau phosphorylation. Insulin also affects vascular reactivity, lipid metabolism, and inflammation to control vascular function (Kellar D et al., 2020). By extreme intake, prolonged excessive insulin/IGF signalling accelerates cellular damage in cerebral neurons. These two factors ultimately lead to the clinical and pathological course of AD (Henderson ST, 2004).

6.1.5 Sulphur-containing amino acids -methionine, homocysteine

Studies suggest that L-methionine, a gluconeogenic amino acid including sulphur that may be converted to s-adenosylmethionine (SAME) via methylation, may help to

improve memory and mental function. S-adenosylmethionine (SAME), is the principal methyl donor in the body responsible for maintaining DNA and myelin integrity. Because of its ability to act as a methyl donor, SAME may undergo a range of vital chemical processes within the body that result in the production of mood-regulating brain chemicals, including serotonin, dopamine, and norepinephrine. However, consumption, whether excessive or insufficient, has an impact on the neurological system and causes short-term memory loss, neurodegeneration, and vascular leakage, which result in the onset of AD.

Homocysteine is an amino acid which contains sulphur that is produced when methionine is converted to cysteine. Multiple studies have found an association between high levels of homocysteine exacerbating neurological problems, resulting in the development of AD and direct brain consequences, which are involved in vitamin B deficiency and the S-adenosylhomocysteine (SAH) conversion process. Overproduction of homocysteine is linked to oxidative damage and DNA destruction in neurons. Further, both endothelial dysfunction and hyperhomocysteinaemia associated with stroke have been connected to cerebral microangiopathy. The lack of source of energy in the brain by stroke leads to neuronal injury, including decreased brain function and cognitive dysfunction (Zhao Y. et al., 2022).

The conversion of S-adenosylhomocysteine (SAH) to homocysteine is revocable. Therefore, high homocysteine may also result in a rise in SAH, which blocks methyltransferase enzymes (including PEMT essential for PC synthesis), further lowering SAME's methylation ability. It impedes the body's natural metabolic activities. SAH is linked to PUFA metabolism, which is linked to AD. Phospholipid metabolism is disrupted by endoplasmic reticulum stress, which is caused by homocysteine. This stimulates sterol regulatory element-binding protein (SREBP), which in turn promotes cholesterol and triglyceride absorption and intracellular (Rogaev EI. et al., 1994). Given that SAME and PC synthesis are both regulated by SREBP-1 and dependent on methylation processes, it follows that dietary or genetic variables that restrict SAME or PC production may activate SREBP-1 and lead to metabolic disorders. Since the trimethylglycine (betaine) alternate route for homocysteine catabolism is inactive due to SAH, methyltransferase enzymes in the brain are also inhibited (Obeid R. et al., 2006).

Therefore, SAH in the CNS must be metabolised to homocysteine before it can be exported, leading to an increase in plasma homocysteine. This explains why the subject of increased homocysteine and illness susceptibility has been so hard to address and shows that SAH may be a harmful metabolite, at least in certain tissues (Miller AL., 2003).

6.2 Main Micronutrients

6.2.1 Water-soluble vitamins

6.2.1.1 Vitamin B

B vitamins play a role in the metabolism of lipids, carbohydrates, and proteins through their function as coenzymes in mitochondrial ATP synthesis. Riboflavin, vitamin B2, and pyridoxine, vitamin B3, are required for B6 metabolism. Niacin(B3) is created from tryptophan by the key enzyme kynureninase, which requires pyridoxal-5'-phosphate (PLP) to active vitamin B6.

Deficiency of the B-vitamin, particularly folate(B9), vitamin B12(Cobalamin) and B6(pyridoxine), can increase homocysteine levels which can increase the risk for AD, heart diseases, and stroke. Homocysteine is a sulphur-containing amino acid that participates in the methionine cycle, acts as a precursor of amino acids such as cysteine and taurine and creates one-carbon methyl groups for transmethylation reactions. A higher level of homocysteine in serum directly shows a neurotoxic effect and is linked to brain atrophy, leading to brain damage and memory decline, resulting in AD.

6.2.1.1.1 Thiamine (B1)

Particularly among the elderly and strong drinkers, thiamine shortage is extremely frequent which is related to neurological problems. In the case of heavy drinkers, alcohol interferes with the passage of thiamine out of intestinal cells, which lowers thiamine absorption. Thiamine-dependent activities are also weakened in the AD brain, which is related to thiamine deficiency (Gibson GE. et al., 2016; Langlais PJ., 1995)

In addition, Thiamine deficiency increases phosphorylated tau levels in cerebrospinal fluid, a biomarker for AD (Gibson GE. et al., 2016). In animal and cellular models, thiamine deficiency promotes the amyloidogenic processing of amyloid precursor

protein (APP) and its accumulation. The relationship between AD and thiamine deficiency in humans requires further investigation.

The consequences of thiamine insufficiency on neurological function can be partially explained by the enzymes that require thiamine as a cofactor. Reduced pyruvate dehydrogenase, transketolase, and ketoglutarate dehydrogenase enzymes in the brain can cause metabolic derangement, leading to low energy supply to neurons and increased oxidative stress. As a result, raised lactic acid and oxidative stress cause abnormal BBB, which leads to neurological toxicity and decreased energy supply to the brain. Further, B1 deficiency leading a decrease in adenosine triphosphate (ATP) synthesis, oxidative damage, and cell death. Cognitive impairment attends the progression due to B1 shortage (Smith TJ. et al., 2021).

6.2.1.1.2 Riboflavin (B2) and Niacin (Vitamin B3)

Vitamin B2 must be supplied by diet since it cannot be created by humans and is mostly stored in the liver, spleen, kidney, and heart muscle as FAD. Consequently, its deficiency may compromise these crucial organs' fundamental functions.

Riboflavin is connected with its conversion into coenzymes such as Flavin mononucleotide (FMN) and Flavin adenine dinucleotide (FAD) in the cell, requiring the synthesis of the redox cofactors, which are essential for the production of ATP in mitochondria and other metabolic processes. Oxidative stress contributes to both the onset and progression of AD. Riboflavin reduces the amount of oxidised glutathione in the body and restores its antioxidant capacity.

Methylenetetrahydrofolate reductase (MTHFR), which is a coenzyme of FAD, is responsible for the conversion of homocysteine to uric acid, xanthine oxidase, and methionine. Elevated homocysteine levels, low reduced glutathione levels, and increased uric acid levels are associated (Seshadri S. et al., 2002). Delaying the development and progression of neurodegenerative conditions like AD may thus be possible through the activation of conserved signalling pathways in humans with vitamin B2 supplementation (Udhayabanu T. et al., 2017).

Unlink other Vitamin B, Niacin (B3) can be synthesised in the human body from an essential amino acid, tryptophan. Vitamin B3 is needed for the synthesis of the

mitochondrial redox coenzymes Nicotinamide adenine dinucleotide (NAD) and Nicotinamide adenine dinucleotide phosphate (NADP), which serve as electron carriers for energy production. In its absence, these coenzymes cannot be produced.

Pellagra, another name for dementia, is caused by a deficiency in either niacin or its precursor, tryptophan. Niacin is necessary for the synthesis and repair of DNA, the myelination and development of dendrites, and the cellular signalling of calcium, and it also functions as a potent antioxidant in the brain's mitochondria (Morris MC. et al., 2004).

6.2.1.1.3 Pyridoxine (B6), Cobalamin (B12) and Folate (B9)

According to Wakimoto and Block, ten per cent of the United States population takes up lower than half of the recommended daily allowance of vitamin B6, and vitamin B6 deficiency is a prevalent condition among the elderly. Vitamin B6(pyridoxine, pyridoxamine, and pyridoxal) is essential since it is a part of the function of the central nervous system. Depletion of Vitamin B6 may be associated with pathology, mood problems, depression, and cognitive impairment. Hyperhomocysteinemia contributes to arterial damage, which is the risk factor for stroke and coronary artery disease and has a direct neurotoxic effect leading to brain atrophy. B6 acts as a crucial cofactor of remethylation of homocysteine properties, supplementation of B6 can lower homocysteine levels in the blood. Lack of them is linked to an increase in blood homocysteine levels, leading to AD, heart disease and stroke (Malouf R. et al., 2003).

Important brain regions have decreased levels of the enzyme tyrosine hydroxylase, which converts tyrosine to L-dopa (a dopamine precursor) in AD. Pyridoxine increases serotonin turnover and tyrosine hydroxylase to enhance hippocampus cognitive function. According to research, NADH(the active form of B3) can result in a sixfold increase in the activity of tyrosine hydroxylase and dopamine (Jung HY. et al., 2017).

Pyridoxal-5-phosphate (PLP), the most active coenzyme form of B6 and most widely used as an indicator of B6 blood levels in the body, is found in supplements, which is critical for the metabolism of amino acids that are used to create neurotransmitters such as aminobutyric acid, dopamine, noradrenaline, and serotonin. Moreover, PLP is needed for the neuromodulatory system and the taurine-generating pathway that initiates with cysteine. Further, it participates in both the one-carbon metabolism and trans-

sulphuration reaction. Without these events, remethylation of homocysteine, which also requires vitamin B12 and folate, is not possible (Kennedy DO., 2016).

Vitamin B12, folic acid (Vitamin B9), and S-adenosylmethionine (SAME) are important for the metabolism of blood cells, the preservation of the central nervous system, and the development of main utilisation of the central nervous system, which includes the brain and spinal cord. It primarily supports the functioning of healthy nerve cells by brain methylation activities (Bottiglieri T., 2013; Lauer AA. et al., 2022).

Age-related health problems can result from dietary deficits, insufficient folate interconversion, and poor absorption. Demyelination may be one of the ways vitamin B12 insufficiency impairs the CNS role. The cofactor for succinyl-CoA, which converts propionate from odd-chain fatty acids to succinate to complete the oxidation phase in the tricarboxylic acid cycle, is adenosylcobalamin an active form of vitamin B12 commonly known as coenzyme B12. In the absence of a sufficient amount of cobalamin, odd-chain fatty acids may be absorbed into myelin, which may impair neuronal transmission (Calderón-Ospina CA. et al, 2020; Metz J., 1992)

Dietary folate can increase the concentration of Docosahexaenoic acid (DHA). DHA is known as omega-3 fatty acid, which is called potential AD treatment. Endogenous Docosahexaenoic acid levels, which are demanding in brain tissue and modify receptor function and cell signalling, also appear to be connected to folate status. Following studies with animals, dietary folate deficit is associated with lower amounts of neuronal DHA. However, a large volume of folate increases the level of DHA by effective migration of methyl groups from SAME to phosphatidylethanolamine (PE), which results in the production of phosphatidylcholine (PC). PC improves cognitive impairments in both people and animals by enhancing learning and memory (Umhau JC. et al., 2006).

6.2.1.2 Vitamin C (Ascorbic acid)

Cognitive impairment is linked to vitamin C deficiency. Patients with AD demonstrated lower plasma levels of vitamin C than healthy people. Vitamin C is an antioxidant which helps to protect the cell against the effect to free molecules and modulator of blood-brain-barrier (BBB) integrity. Vitamin C builds up in the brain and central nervous system, where it is far more abundant than in plasma or other organs. The effects of ascorbic

acid supplementation included an extension of life span and a reduction in cell proliferation, oxidative stress, chromatin disorder, and excessive inflammatory factor release.

In the brain, vitamin C act as a neuromodulator that protects the cell and helps with neuronal maturation, leading to generating brain cells and creating and maintaining neuronal connection. In the animal model, greater ascorbic acid intake for six months in AD mice demonstrated a positive effect, offsetting beta-amyloid oligomerisation and behavioural decline but not reducing brain plaque deposition. However, transgenic mice which eliminate L-gulono- γ -lactone oxidase (GULO), which is an essential enzyme for ascorbate biosynthesis, showed decreased amyloid plaque deposition in response to high dosages of vitamin C supplementation (Kook SY. et al., 2014).

6.2.2 Fat-soluble vitamin

6.2.2.1 Vitamin A (*Retinol, Retinal, Retinoic acid*)

AD and vitamin A, retinoic acid has a strong linkage. Cognitive impairment has been demonstrated to be impacted by vitamin A deficiency, which involves increased levels of amyloid-beta secretase (Zeng J. et al., 2017), impaired cholinergic transmission and inflammation of the nervous system that causes microglia activation. The activation of microglia is one of the causes of AD (Das BC. et al., 2019). Microglia dysfunction may alter the retinoic acid content in a certain area (Khatib T. et al., 2020). Additionally, vitamin A and its metabolite attaches to retinoid X receptors (nuclear receptors) in lipid metabolism and has a hormonal effect, playing a significant role in the adult cell proliferation, differentiation of nerve cells, the production of neurotransmitters in the brain, and gene expression (Zieger E. et al., 2017). Retinoid X receptor is a coactivator of peroxisome proliferator-activated receptors (PPARs), which control lipid metabolism genes (Wójtowicz S. et al., 2020). Resulting in vitamin A shortage causing decreased phosphatidylcholine (PC) synthesis and fatty acid availability, leading to a decrease in hepatic phospholipids. This means that this might disrupt phospholipid formation in the brain and interfere with lipid metabolism in the liver, which would impact the generation of bile (Oliveros LB. et al., 2007)

The ADAM 10 gene, which has been shown to be controlled by retinoic acid, encodes the disintegrin and metalloproteinase protein ten that is mostly expressed in neurons of the cerebral cortex, hippocampus, and cerebellar granular cell in the central nervous system. Increasing alpha-secretase ADAM-10 activity in the brain promotes cleaving off the amyloid-beta precursor protein (APP) in the non-amyloidogenic signalling pathway that produces APP-derived fragments, which can protect APP deposition. In the vitamin A-deficient animal model, impaired ADAM-10 transcriptions were seen in AD-treated animals. Supplementation with vitamin A increased transcription of both ADAM-10 and raised levels of neuroprotective secretory (Peron R. et al., 2018). However, deficiency in vitamin A in adult rats causes more amyloid to accumulate in brain arteries (Husson M. et al., 2006).

Inflammation is a hallmark of AD. Retinoic acid is a potent immune modulator that decreases Amyloid-induced inflammation by blocking Interleukin-6 (IL-6) and Tumour Necrosis Factor- α (TNF- α) and by raising the production of anti-inflammatory cytokines such IL-10 (also known as anti-inflammatory cytokine) (Das BC. et al., 2019). Potentially attributable to NF- κ B suppression are these results. NF- κ B is a nuclear factor kappa-light-chain-enhancer that is involved in inflammatory, immune response, and regulates transcription of DNA, which is related to cell survival, proliferation, and differentiation (Austena LM. et al., 2004)

To maintain proper mitochondrial energy balance, retinol is required as a cofactor for the enzyme protein kinase C-delta (PKC-delta), which is involved in cellular processes such as apoptosis, proliferation, transcription, and signal transduction. More ATP is generated when protein kinase C-delta is activated by retinol, which in turn triggers pyruvate dehydrogenase to enhance pyruvate input into the tricarboxylic acid cycle (Kim YK. et al., 2020; Acin-Perez et al., 2010). This suggests that the hypometabolism seen in the AD brain may be at least partially due to vitamin A deficiency (Kim YK. et al., 2020).

6.2.2.2 Vitamin D (Calciferol)

Vitamin D also plays an essential role in the neurogenerative process. Low vitamin D levels in older persons are linked to an increased risk of cognitive deterioration, multiple sclerosis, Parkinson's disease, dementia and AD. Vitamin D has the power to diminish

hippocampus-related inflammation and prevent the build-up of amyloid in response to enhancing phagocytosis. Vitamin D receptor mRNA is lower in AD than in controls in some parts of the hippocampus, and polymorphisms in this receptor are more common in AD. The active form of vitamin D3, which is 1,25-dihydroxy vitamin D3, inhibits inducible nitric oxide synthase, therefore decreasing inflammation and oxidative stress and blocking hyperactivation of microglia (Landel V. et al., 2016).

Research shows that people with AD had reduced amounts of vitamin D and greater levels of parathyroid hormone (Sato Y. et al., 1998). In order to regulate blood calcium levels, parathyroid hormone is generated. An imbalanced level of calcium level can cause an abnormal level of parathyroid hormone, leading to hypoperfusion, osteoporosis and impaired neural signalling. Regulation and maintenance of calcium homeostasis are important of vitamin D supplementation that controls calcium channel function by decreasing beta-amyloid deposition and avoiding excitotoxicity. The expression of vitamin D receptors is also increased, which has an additional antioxidant impact. Calcium ion is a key second messenger in the growth and development of brain nerve cell cells in the brain, compromising synaptic and cognitive function. According to the study, disturbance of intracellular calcium homeostasis, particularly abnormal and extreme release from the endoplasmic reticulum via ryanodine receptor (RyR), is the key factor that accompanies memory loss and cognitive impairment. Due to the abnormal calcium ion (Ca^{+2}), release through RyR leads to increased β -secretase and γ -secretase activities, causing the production of Amyloid- β deposition (Wang Y. et al., 2017).

Further, enhanced voltage-gated Ca channels, decreased Ca-buffering capacity, and the neurotoxicity of glucocorticoids all contribute to the death of hippocampus cells in AD. Insulin sensitivity and signalling are both influenced by vitamin D. Low testosterone in older men has been linked to mild cognitive deficiency and AD, and research of almost 2,000 men indicated an association between levels of vitamin D and bioavailable testosterone. Vitamin D has been demonstrated in animal research to have a crucial role in gonad function and sex hormone synthesis (Kinuta K. et al., 2000).

Glutathione is an intracellular antioxidant that is synthesised in higher amounts when vitamin D is present. A low amount of glutathione in the hippocampal region of the brain causes mild cognitive impairment, leading to AD.

Neurotrophins are the important mediators in the central nervous system, which help to keep nerve cells healthy and alive by regulating of development, maintenance, proliferation, and function of the nervous system. Since the low level of vitamin D decreases the production of neurotrophins such as neuroprotectin D1, docosanoid, and glial-derived neurotrophic elements (Buell JS. et al., 2008), leading to an increasing amount of neuron death and preventing dendrite growth.

6.2.2.3 Vitamin E

Vitamin E is a potent antioxidant that relieves oxidative stress in beta-amyloids. Further, Vitamin E has long been known to prevent lipid peroxidation and modulate gene expression, but new research shows that it also prevents the intracellular build-up of ceramides and cholesterol (Cutler RG. et al., 2004).

Low levels of vitamin E are connected with worse memory in the elderly. Considering that oxidative stress performs a major role in the formation of beta-amyloid deposition, which is the critical factor that leads to AD. Beta-amyloid induces oxidative stress leads to harmful effects on the synapse and neurons by boosting the formation of the reactive oxygen species (ROS), lipid peroxidation, protein oxidation, and tau hyperphosphorylation (Gugliandolo A et al., 2017).

Neuronal culture cells are protected against apoptosis by vitamin E when exposed to the toxin amyloid (Yatin SM et al., 2000). Plasma vitamin E is carried there by phospholipid transfer protein. Vitamin E transport to the brain may be impaired and oxidative stress elevated due to decreased phospholipid transfer protein activity in AD (Desrumaux C. et al., 2013)

Vitamin E deprivation has been shown to cause abnormal gene expression in the hippocampus of rats, according to gene array research. Decreased expression of amyloid-clearing genes was seen in vitamin E insufficiency (Gugliandolo A. et al., 2019).

6.2.3 Minerals elements -metal ions

Multiple investigations have discovered that metal ions contribute to many clinical disorders, including immune dysfunction and AD. Inflammation is known to contribute to the risk and progression of Alzheimer's disease. Zinc, copper, and iron are the main ions that are linked to AD and connected to amyloid and tau metabolism and maintain the proper function of the cell membrane. The elderly are at increased risk for Zn insufficiency, and Cu may affect Zn intake and status (Schrag M et al., 2011)

In an animal model of Alzheimer's disease, zinc deficiency worsened cognitive decline because of an enhancement in NLRP3(inflammasome) that activate proinflammatory cytokines that drives inflammation. This causes cellular damage and microbial infection (Rivers-Auty J et al., 2021).

Cerebrospinal fluid and brain Zn levels are reduced in AD, and serum Zn levels are negatively linked with senile plaque count. Zn shortage may be indicated by plasma levels, but Zn homeostasis is regulated differently in the brain. Therefore elevated brain Zn levels may be normal (Loef M. et al., 2012). However, tissue Zn depletion is a hallmark of AD, and this is compounded by abnormal cellular Zn mobilisation and a possible elevation of Zn/Cu superoxide dismutase (SOD) in afflicted regions. Both Zn and Cu ions are engaged in the SOD mechanism. The copper zinc superoxide dismutase (Metalloprotein) is an enzyme that possesses a potent antioxidant function that mitigates oxidative stress, but its overexuberant release (flooding) in reply to oxidative stress may amplify amyloid toxicity and trigger apoptotic processes, which leads to neuron death (Massaad CA. et al., 2009). Zn metalloproteinase, which degrades amino acids and plasma insulin levels, is present; its isoform is found in mitochondria (Loef M. et al., 2012). Low Zn levels may decrease the activity of this enzyme, hence decreasing amyloid clearance.

Lipid and fatty acid metabolism are influenced by Zn. A higher concentration of the zinc transporter protein ZnT3, which is responsible for loading zinc into synaptic vesicles, and a lower concentration of zinc in the blood plasma are observed in animals grown on diets low in n-3 polyunsaturated fatty acids (Jayasooriya AP. et al., 2005). DHA treatment of neuroblastoma cell lines resulted in decreased apoptosis, Zn absorption, and ZnT3 expression. Desaturase activity (needed for DHA generation) may increase in DHA-depleted cells since Zn is a cofactor for desaturase. This would result in more long-chain

PUFA being produced. Fatty fish are high in zinc, docosahexaenoic acid (DHA), and vitamin D (which improves intestine absorption of Zn).

With ageing, the amount of iron in the brain gradually rises. The iron level in the brains of AD patients was surprisingly discovered to be considerably higher with magnetic resonance imaging (MRI). Iron is a necessary component for cellular life, including biological processes like electron transfer. It may take or provide electrons as ferrous iron transitions between the divalent, ferric, and tetravalent iron states, acting as a catalytic cofactor in some biochemical processes. Additionally, iron, in the form of iron-sulphur clusters (Fe-S), stimulates the activity of several biological enzymes involved in DNA replication and repair (Peng Y. et al., 2021). Iron is also a component of haemoglobin and myoglobin, two substances that help organisms transfer oxygen and carbon dioxide. If iron is lacking when the brain is developing, it will result in permanent developmental delays. Nevertheless, if iron excess, due to the iron homeostasis disruption, exerts neurotoxic effects, it will harm the brain's normal physiological functions by boosting beta-amyloid deposition and neurofibrillary tangles formation (Liu JL. et al., 2018).

7. PATHOPHYSIOLOGY FACTORS RELATED TO THE GASTROINTESTINAL TRACT

7.1 Oral health and *Porphyromonas gingivalis*

Porphyromonas gingivalis is a major anaerobic pathogen in periodontitis which is an inflammatory periodontal and gingival disease that damages both bone and supporting soft tissue of bone. In addition, in the supporting evidence, periodontitis has been discovered in the atherosclerotic plaques (Brodala N et al., 2005), and systematic peptic ulcer which is also involved in systemic diseases (Hayashi C et al., 2010).

Gingipains are a part of toxic cysteine proteases that are secreted from the bacterium *P. gingivalis*, involved in the regulation of host inflammatory response. This plays a potential role in the development of AD pathogenesis and the growth and survival of the *P. gingivalis*. The level of gingipain is correlated with tau and ubiquitin pathology. Nuclear factor Kappa B and ubiquitin were also found in the same part as gingipains fragment tau. Due to the neurotoxic effect of gingipain showing negative effects on tau, which is required for appropriate neuronal function. Tau is fragmented by gingipain, forming hyperphosphorylated Tau that leads to neurodegeneration which is shown to correlate with cognitive impairment of AD (Leblhuber F et al., 2020). Small protein ubiquitin accumulates in both tau tangles and beta-amyloid plaques that tag damaged proteins for degradation. To prevent neurotoxicity, needed to develop and synthesise small-molecules inhibitor to target gingipains. Gingipain inhibitor can prevent several beneficial effects such as reducing bacterial deposition in the brain infection, blocking beta-amyloid deposition, reducing neuroinflammation, restore hippocampal neurons, which is a potential treatment for neurodegeneration of AD and bacteria colonisation in the brain.

Due to the bacterial infection in the brain, increased production of $A\beta_{1-42}$, which has antibacterial effects, accumulated in response to gingipain, resulting in amyloid 1-42 brain deposition. According to research conducted by Dominy et al., oral *P. gingivalis* led to an increase in the AD marker beta-amyloid 1-42 ($A\beta_{1-42}$) in mice. $A\beta_{1-42}$, extracellular plaques were observed in non-transgenic C57BL/6 mice after chronic oral administration of *P. gingivalis* induced experimental chronic periodontitis. Not only C57BL/6 mice, but

also orally *P. gingivalis* treated wild-type mice also showed the negative effect that exhibit neurofibrillary tangles of hyperphosphorylated tau protein production, neurodegeneration, and neuroinflammation. This is followed by the loss of neuronal cells, which mainly affects the cerebral cortex and hippocampus leading to AD (Dominy SS et al., 2019; Ilievski V et al., 2018).

High serum immunoglobulin (IgG) level and *P. gingivalis* are closely related, according to Sparks Spein et al researchers. A 2009 study found that periodontitis patients with *P. gingivalis*, showed high levels of IgG and lower verbal memory and subtraction test scores than in individuals without *P. gingivalis*. *Gingivalis* was found to be associated with AD via IgG antibody serum in a second longitudinal study, confirming the findings of the first study (Noble JM et al., 2009; Noble JM et al., 2014).

Using APP-transgenic (APP-Tg) mice, Ishida N et al. wanted to determine whether periodontitis worsens AD. In a study comparing mice with and without periodontitis, researchers discovered that mice with periodontitis possessed significantly inferior cognitive abilities. APP-Tg animals contained more beta-amyloid and the pro-inflammatory cytokines IL-1beta and TNF-alpha than control mice and lipopolysaccharide (LPS) from *P. gingivalis* had the potential to worsen A β accumulation, thereby increasing neuroinflammation. Pro-inflammatory LPS is a bacterial-derived neurotoxin and genotoxic that affects brain tissue, supporting inflammatory neurodegeneration and failure in homeostatic gene expression by stimulating amyloid beta 42 peptide deposition and production of TNF- alpha and IL-1 production in neuron cell cultures in vitro (Ishida N et al., 2017).

Middle-aged mice infected with *P. gingivalis* had an increase in brain-inflaming TNF-alpha, IL-6, and IL-1. However, in this study, *P. gingivalis* had no discernible effect on the young mice (Ding Y et al., 2018). *P. gingivalis* and its constituents are linked to neuroinflammatory and neurodegenerative processes, including the formation of Amyloid-beta plaques and hyperphosphorylated Tau, according to studies in mice and humans (Olsen I et al., 2015).

7.2 Role of oral health in AD and possible alternative treatment

Along with cognitive impairment, one's dental health declines. Reduced cognitive function in AD makes it more challenging for them to consistently practice good oral hygiene to aim to decrease the possibility of growth of AD-induced-bacteria (Kamer AR et al., 2009; Harding A et al., 2017)

According to the research, poor dental hygiene and periodontitis are linked to cognitive decline that increase the risk of neurodegenerative diseases such as dementia and AD by 22 to 66 percent. Periodontitis, a shift in the balance of commensal microbial communities in the mouth, and an increase in the virulence of *P. gingivalis* or/ and Spirochetes are all linked to inadequate oral hygiene practices. Trying to stabilise periodontitis and lowering systemic exposure to *P. gingivalis* can reduce the disease progression of AD. To reduce the severity of any existing conditions, it is essential to maintain regular dental visits and good oral hygiene practices. (Harding A et al., 2017)

7.3 Gut Microbiome

In 2001, Lederberg and McCray introduced the term "microbiome" to refer to the unique microbial ecosystem of the human body, which includes both beneficial and pathogenic microorganisms (Prescott SL., 2017). It relates to a group of microorganisms such as fungi, bacteria, and viruses that present in a particular environment. It is estimated that between 10 and 100 trillion symbiotic microbial cells reside in the body, with most of them located in the digestive tract, which is known as the gut microbiome (Ursell LK et al., 2012). The Human Microbiome Project studied the microbial community composition at multiple body locations (Grice EA., 2012), which was started in 2007 to investigate the role of beneficial bacteria in human health (Blum HE., 2017). A positive effect of microorganisms on health includes immune system regulation, protection against other pathogenic bacteria and assistance with digestion. Microbiotas colonise the oral cavity, skin, gastrointestinal system, and genital tract (Kennedy MS., 2020).

Intestinal bacteria can affect brain function and accelerate neurodegeneration through a number of mechanisms. Due to the activity of the immune system, the regulation of gut bacteria alters not only gastrointestinal disorder but also central nervous system diseases such as AD by interacting between the immune and nervous systems. Such microbes, *Bacteroides fragilis* and *Escherichia coli*, which are the prevalent bacteria in

the gastrointestinal tract that mainly play a role in the stress-induced secretion of a complex mixture of bacterial amyloids, endotoxins and exotoxin and lipopolysaccharides (LPS) (Lukiw WJ., 2016).

According to the research, the blood-brain barrier's integrity is negatively impacted by changes in the composition of the gut microbes due to dysbiosis, which increases intestinal permeability of the gut barrier and immune activation leading to systemic inflammation, which promote blood-brain barrier damage that provokes neuroinflammation, neural injury and neurodegeneration. Increased blood-brain barrier permeability can generate excessive amyloids and LPS secretion, which may change the signalling pathway and create proinflammatory cytokines that induce inflammation which is linked to AD pathogenesis (Askarova S. et al. 2020; Jiang C. et al., 2017)

Hyperstimulation of the immune system in the elderly that associated with a persistent inflammatory condition of gut mucosa that leads to a change in gut microbiota composition that decreases diversity and stability. The persistent inflammatory condition can break down the gut barrier that increases proinflammatory cytokinin leading to AD.

Microbiota-gut-brain axis through the Vagus nerve is a bidirectional communication network between gut bacteria and the brain that is implicated in multiple biological systems such as neural, immune, endocrine, and metabolic pathway. Disturbance along the axis may contribute pathogenesis of AD (Kowalski K. et al., 2019).

8. RISK FACTORS OF INFECTIONS

8.1 Virus – Family *Herpesviridae*

Herpesviridae is a DNA virus family; 8 members (HSV-1, HSV-2, HHV-6, CMV, VZV, EBV, HHV-7, and HHV-8) infect humans and cause infection and neurological disease. Herpes simplex virus type 1, 2 (HSV-1,2) and cytomegalovirus (CMV) are the most researched viruses in the family *Herpesviridae* that are linked to cognitive impairment (Watson AM et al., 2013). The aggressive antiviral drug is one of the potential treatments to reduce the risk of neurological disorders involved in the virus (Devanand DP et al., 2020).

According to recent studies, herpesvirus infections can cause the development and deposition of tau and beta-amyloid in the brain neuron, which is caused by activation of the body's natural defence mechanisms against microorganisms (Eimer WA et al, 2018).

HSV-1 is typically transmitted by oral-to-oral contact and causes infection in the mouth. By ageing blood-brain barrier can be loosed, resulting in viruses that can invade the central nervous system. The body's natural defence is related to the inflammatory process. Inflammation is the immune system's response to harmful stimuli such as viruses. Once the virus enters the brain, it initiates the healing process which is called inflammation. Then up-regulate both beta- and gamma-secretase that contain A β -producing properties (Wozniak MA et al., 2007). Since beta-amyloid has an anti-viral effect, deposit on the viral leads to beta-amyloid deposition, leading to neurodegeneration (Eimer WA et al, 2018).

Genetical factors can increase the risk of virus exposure. Apolipoprotein E epsilon 4 (APOE e4) is the strongest genetic risk factor for the late onset of AD. 10-15% of people with the APOE4 gene develop neurodegenerative disorder and AD (Michaelson D.M. et al., 2014). This protein combines with lipids in the body to form lipoproteins which can carry into the bloodstream. According to research, APOE 4 disrupt endocytosis due to its induced ER-stress in astrocyte where APOE4 is produced (Schmukler E et al., 2018).

When a virus is associated with APOE4, that impairs the ability of APOE4-expressing glia to clear beta-amyloid leading to beta-amyloid production (Ries M et al., 2016).

8.2 Bacteria involved in periodontal infection

According to a recent study, AD brain samples contained bacteria associated with periodontal disease and gingivitis (Siddiqui H et al., 2019). In the study of the periodontal infection, predominately, gram-negative anaerobic bacteria may include such *Porphyromonas gingivalis*, *Treponema spp.*, *Aggregatibacter actinomycetemcomitans*, *Tannerella*, *Prevotella intermedia*, and *Fusobacterium nucleatum* (Kamer AR et al., 2009). *P. gingivalis* and Spirochetes are the anaerobic bacteria that most often cause periodontal infection, leading to AD. Antibodies against *P. intermedia* and *F. nucleatum* were found to be significantly higher serum levels ($p = 0.05$) in AD patients, according to a second rigorous serological study (Sparks Spein P et al., 2012). According to Beydoun et al., AD may be affected by periodontal and *Helicobacter pylori* infection (Beydoun MA et al., 2020).

8.2.1 Porphyromonas gingivalis

P. gingivalis a gram-negative bacteria that cause periodontitis related to the gastrointestinal tract. This releases gingipain which is a toxic protease that is related to neurodegeneration and neuroinflammation, by affecting both gut and brain barriers that lead to damage of neurons in the brain via systematic circulation (Hayashi C et al., 2010).

8.2.2 Spirochetes

Infection by spirochetes, periodontal bacteria which is involved in the slowly progressive AD by attracting the innate immune system. Concerning Miklossy's research, various types of spirochetes, gram-negative bacteria such as *Treponema pallidum* and *Borrelia burgdorferi* compromise the pathogenesis of AD (Miklossy J et al., 2015). Multiple *Treponema* species were also discovered in various regions of AD patients' brains. In the brains of people with AD, peptidoglycan was also found close to beta-amyloid deposits, and spirochetes were visible in neurofibrillary tangles and senile plaques. A highly prevalent periodontal pathogen, *Treponema pallidum*, was detected in 90% of AD cases. However, *Borrelia burgdorferi* was founded in the brain in 25,3% of AD cases (Miklossy J, 2011).

When the disruption of the dental plaque occurs, tooth microbes will move from the oral cavity through the bloodstream, which leads to bacteraemia (increased level of the bacteria in the blood). Due to the preference for neural tissue, it can easily cross the blood-brain barrier, entering to the brain. Once spirochetes reach the brain, forming a biofilm to ensure their survival. The body's innate system is activated to destroy biofilm, and then forms a Toll-like receptor (TLR2). The final result of the biofilm is converted to beta-amyloid with beta-amyloid converting enzyme (BACE), leading to beta-amyloid load, resulting in the neurocircuitry of the brain. (Spirochetes → biofilm → TLR 2 → TNF- α → Beta & gamma secretase → APP → beta-amyloid) (Allen HB., 2016)

8.3 Fungi

Candida albicans grow in the human gut, mouth, and vagina naturally. When this yeast reaches another organ via systematic circulation, it can cause serious infection. This fungus can cross the gastrointestinal barrier that, changes the composition of the gut microbe and damage the gut barrier, which is the pre-deposition region of the fungal brain infection. Resulting in *C. albicans* travelling to the brain via- the gut-brain axis, inducing inflammatory responses. Further, an extremely selective barrier, the blood-brain barrier (BBB) lets only a small number of undesirable chemicals get through. *Candida albicans* is one of these fungi, that can penetrate the BBB and cause infections, leading to AD thorough inflammatory response (Parker A et al, 2022).

Ageing and respiratory infection such as asthma are more vulnerable to this disease. Increasing the age, leads to a poor adaptive immune response that may contribute to the emergence of fungal infections. Due to the antimicrobial properties of the beta-amyloid, that fight against fungus *C. Albicans*, resulting in the formation of beta-amyloid plaque, which is the main factor of AD pathogenesis.

Beta-glucan is one of the numerous components of the fungal cell wall polysaccharides, which consist of 50-60%. Anti-beta-glucan antibodies are founded in healthy humans, which can develop to regulate fungal pathogenesis. In contrast to healthy humans, the level of the fungal antigen is used to detect and test for fungal infection. Patients with systemic candidiasis observed circulating fungal antigens(beta-1,3-glucan), and immunoglobulin G (IgG) antibodies against these antigens (anti-cell wall) were examined,

according to this study. Chitin and DNA were also detected in the patient's brain tissue. Chitin is a polymer found on fungi cell walls which were detected in AD brains. Utilizing certain antibodies to detect various fungi, fungal material may be found both within and outside of cells. To prevent and decrease the progression of fungus related-AD needed to use antifungal treatment (Parady B, 2018)

9. NUTRITION FOR PREVENTION THERAPY

9.1 Cholesterol, saturated fat, and trans-fat reduction

High intake of cholesterol, saturated fat, and trans fats are related to AD development. According to ecological studies, consuming animal products is strongly associated with AD (Grant WB., 2016). According to the Chicago Health and Aging Project, persons who consumed the most saturated fat had a greater than twofold risk of acquiring AD (Morris MC, 2004; Morris MC et al., 2014). Two food sources that are particularly high in saturated fat are dairy and beef. Dairy products and snack foods contain trans fats (Physicians Committee for Responsible Medicine, 2021).

It is possible that the amount of fat in the diet affects the amount of cholesterol in the blood (Morris MC, 2004). Middle-age hypercholesterolemia is connected to a heightened risk of AD. In recent research, cholesterol metabolism and AD pathologies are related. In the animal model with AD transgenic mouse with high cholesterol diet showed an increased level of beta-amyloid peptide deposition by raising both size and number of peptides (Lorenzo M. et al., 2000, Gillette Guyonnet S. et al., 2007). Ghee, dry milk, beef, cheese, and eggs all contain oxidized cholesterol, which, after crossing the blood-brain barrier, may contribute to AD by triggering neuroinflammation and free radical generation. Animal products are a major source of prostaglandin E (PGEs), which is involved in a toxic inflammatory response, leading to beta-amyloid load, linked to AD development. A higher proportion of unsaturated to saturated fat is linked to a lesser risk of cognitive deterioration or AD. A meta-analysis of fish and omega-3 fatty acid consumption revealed a 36% reduction in the risk of AD (Physicians Committee for Responsible Medicine, 2021).

Several studies and meta-analyses have demonstrated that a Mediterranean diet offers cognitive benefits to avoiding and preventing AD pathogenesis by diet. These diets compromise less dairy and meat, including fruits, vegetables, and whole grains than Western diets, which consist prevalence of saturated fat such as red meat, high-fat dairy products and processed foods (Gamba P. et al., 2015). The main source of fat in the Mediterranean diet is olive oil, which is one of the unsaturated fat made of oleocanthal. Oleocanthal is a natural phenolic compound which is a potent antioxidant and natural

anti-inflammatory product through the COX system that help to block and destroy beta amyloid deposition and inhibits tau protein fibrillization, which can protect against AD and related dementias (Swaminathan A., 2014; Tajmim A. et al., 2021).

Instead of a high saturated and trans fat diet, soy-based foods can also be substituted, which are prevalent in Asian cuisine and cholesterol-free that contain less saturated fat than animal products. In soy milk and tofu, we may find soybean's high nutritional content, which includes vegetable protein, oligosaccharides, dietary fibre, vitamins, and minerals. Due to the high content of isoflavone phytoestrogen in the soy-based foods that bind to oestrogen receptor agonists, shows beneficial effects on several disorder such as oestrogen replacement therapy in postmenopausal women and memory disorder by improving learning, spatial memory, and function of the brain. Owe to its various functions, soybean both enhance cognitive functioning and reverse memory loss which can use to improve AD (Physicians Committee for Responsible Medicine, 2021). Isoflavones have also been found to be potent anti-inflammatory and antioxidant agents (Hsieu HM et al., 2009).

9.2 Management of weight

Maintaining ideal body weight is essential to prevent and reduce the progression of AD and other diseases, including heart disease, diabetes, and some cancers. Middle-aged people with high body mass index (BMI) or obesity are closely connected to AD (Whitmer RA. et al., 2005).

A high body BMI level (normal BMI in adults 18,6-24,9) or obese patients have an excessive number of adipose tissues that promote lowered blood flow to the brain, affecting cerebral vascularization. Inadequate cerebral blood circulation can cause vascular injury, resulting in brain ischemia in the sensitive and vulnerable brain areas such as the hippocampal and cerebellum (Dake MD et al.,2021). When ischemia occurs in the susceptible hippocampus area, decreased oxygen and glucose intake will be shown due to the hippocampus' baseline metabolic activity, leading to memory loss (Kivipelto et al., 2005). Dysfunctional adipocytes are introduced by increasing the number of adipocytes due to increased body weight and decreased physical activity. Adipokines such as leptin, adiponectin, and interleukin-6 are the cytokines produced by

dysfunctional adipocytes and play a role in inflammation and obesity. This factor can produce chronic peripheral inflammation that can spread to the brain, leading to neuroinflammation that expresses a negative impact on the brain white matter, which impairs neuronal connections (Arnoldussen IA et al., 2014; Kiliaan AJ et al., 2014).

9.3 Antioxidants, nutritional supplements

Supplementing with a potent antioxidant like vitamin E, vitamin C, or beta-carotene helps fight off the free radicals, which could injure brain cells, preventing or reducing the harmful effects of free radicals that can delay the course of AD.

9.3.1 Vitamin E in diet

Vitamin E is a fat-soluble molecule, having anti-oxidant properties that consist of four tocopherols and four tocotrienols. Most studies suggest that alpha-tocopherol is used as an antioxidant in AD (Gugliandolo A, 2017). AD neuropathology may be influenced by the lower levels of tocopherol in AD CNS tissue compared to normal controls (Morris MC et al., 2015). According to the Chicago Health and Aging Project, 14.3% of the elderly with low vitamin E consumption had AD, while only 5.9% of the elderly with a high vitamin E intake through diet (as opposed to supplements) developed AD (Morris MC et al., 2002). Those who consumed the most vitamin E reduced their risk of acquiring AD and other types of dementia by 25% over the following years, according to a Dutch study of 5,395 individuals aged 55 and older (Devore EE et al., 2010).

Vitamin E is rich in foods such as vegetable oils (olive, canola oil) and fats, nuts and seeds. Which also possible to intake concentrated form of vitamin E in the form of oral supplement in capsules or drops. A randomized clinical study revealed that people with AD benefited from a high vitamin E dose (2,000 IU daily for two years) (Dysken MW et al., 2014).

9.3.2 Vitamin C in diet

Vitamin C is produced during glucose metabolism. Due to the water-soluble properties, compared to vitamin E, vitamin C is commonly safe that does not deposit in the body. A high dose of vitamin C significantly decreases the plaque deposition in the cortex by 57,9%

and the hippocampus by 40,29% in the animal model (Lim GP et al., 2005). The fact maintaining a healthy or high level of vitamin C level showed a protective function against both AD and cognitive decline (Travica N et al., 2017).

Patients with moderate cognitive deficiency and AD had lower vitamin C levels than healthy controls. Vitamin C-rich foods may lessen the risk of AD since higher intakes (via diet and low-dose supplementation of 500 mg or less per day) may prevent cognitive decline (Harrison FE, 2012). Since vitamin C is absorbed at a rate of approximately 400-500 mg per day, greater dosages are probably not more useful (Levine M et al., 2001). The greatest sources of vitamin C are fruits and vegetables, particularly citrus (citrus fruits like oranges, kiwis, lemons, and grapefruit), bell peppers, and cruciferous vegetables (broccoli, cabbage).

9.3.3 Beta-carotene

The natural pigment beta-carotene may be found in leafy green, yellow, and orange fruits and vegetables (such as carrots, spinach, lettuce, tomatoes, sweet potatoes, broccoli, cantaloupe, and winter squash). The more beta-carotene a fruit or vegetable possesses, typically, the more intense the colour. Due to its antioxidant abilities, it also offers defence against potentially harmful chemicals like free radicals that can delay the development of AD (Hira S et al., 2019).

Retinoic acid, a component of vitamin A, and AD are also closely related. Vitamin A is a precursor of beta carotene. Vitamin A deficiency has been shown to have an influence on cognitive impairment (Zeng J. et al., 2017). This is due to higher levels of amyloid-beta secretase, decreased cholinergic transmission, and nervous system inflammation that results in microglia activation (Das BC. et al., 2019).

9.4 *Micronutrient adequacy*

Those with AD had significantly decreased levels of vitamins A, B12, C, E, and folate, while levels of vitamins D and zinc were unaffected. The results held true even in AD patients who were not malnourished (Devore EE et al., 2010). Individual metals such as copper, zinc, aluminium and magnesium have been suggested as potential risk factor of AD since these metals are directly connect with APP metabolism or with APOE (A

Armstrong R, 2019). Many minerals are deficient in AD patients, so a multivitamin may be beneficial if it does not contain iron or copper. Many minerals are deficient in AD patients, so a multivitamin may be beneficial if it does not contain iron or copper. In addition, exposure to aluminium, which is neurotoxic metal, is also a possible suspect in AD (Huat TJ et al., 2019).

9.4.1 Copper avoiding

A meta-analysis found that AD patients who avoided copper consumption had a higher total copper body burden than the general population. AD patients have an impaired copper metabolism, resulting in an abnormally high concentration of free copper (ceruloplasmin) (Ventriglia M et al., 2012). Unbound copper concentrations in the brain are rising (Squitti R et al., 2014). Copper levels in the brain increase with age, which is cause for concern because copper promotes the synthesis, aggregation, and neurotoxicity of amyloid beta precursor protein (APP) (Harris CJ et al., 2014).

9.4.2 Iron avoiding

Some research suggests that an elevated iron level may increase the risk of, due to the electron donor and acceptor properties of the iron, excessive iron easy to causes oxidative stress leading to the form of beta-amyloid plaque and neurofibrillary tangles in the presence of iron in the brain (Liu JL et al., 2018).

Iron homeostasis, the transfer of iron from the blood to the brain, is strictly regulated (Peters DG. et al., 2015). Disruption of the iron homeostasis occurs due to genetic and environmental factors or ageing, leading to iron metabolism diseases such as AD. By ageing, the blood-brain barrier has loosed that start clinical symptoms by crossing the iron into the brain. Further, iron may accumulate in the brain due to the impact of the Western diet on the blood-brain barrier (Hsu TM. et al., 2014). The western diet contains animal-based food like meat and eggs which are rich in iron. The genetic factor that human has Apolipoprotein E (APOE) gene, is the strongest genetic risk factor if cognitive disorders and AD that is involved in fat metabolism in the body that makes a protein that carries cholesterol and other types of fat in the bloodstream. There was a significant correlation between ferritin levels and apolipoprotein E in cerebrospinal fluid, and the

APOE-4 allele was associated with elevated ferritin levels, suggesting that excess iron in the brain contributes to the onset and progression of disease (Ayton S. et al., 2015).

Typically found in multivitamin/mineral supplements are copper and iron. Dietary supplements absent these minerals and decreasing the amount of high content iron diet are important to prevent the prevalence of AD. As a result, iron-targeted therapy approaches have emerged as a unique AD treatment (Peng Y. et al., 2021).

9.4.3 Aluminium avoiding

In contrast to iron and copper, aluminium is not essential to human biology. Due to the non-essential nutrient, also called systemic toxicants, the high amount of aluminium can severely impact human health, such as organ damage, immune system dysregulation and AD pathogenesis (Huat TJ. et al., 2019). High exposure to aluminium-rich dust (A Armstrong R., 2019) or/and the presence of aluminium in water supplies leads to accumulation in the neurofibrillary tangle-bearing neurons. Due to the neurotoxic properties, this can go through BBB, leading to beta-amyloid aggregation (Huat TJ. et al., 2019).

9.4.4 Supplemental vitamin D level

A meta-analysis revealed that the incidence of AD and dementia was 21 per cent higher in those with inadequate vitamin D blood levels (50 nmol/L) than in those with adequate levels, indicating a link between vitamin D deficiency and global cognitive decline in adults. Vitamin D deficiency is also more prevalent in Alzheimer's disease patient (Shen L. et al., 2015).

9.5 Alcohol consumption at the healthy level

However, a meta-analysis revealed that light to moderate drinkers have a 30 per cent lower risk of AD and a 25 per cent lower risk of dementia than non-drinkers. Although even 20 g/day (1.25 servings) of alcohol is a risk factor for particular hypertension, cancers, and other disorders, this is the case (Rehm J. et al., 2003). Moderate alcohol consumption may reduce cardiac risk factors (platelet aggregation or blood lipids) and stimulate the production of acetylcholine in the hippocampus. The hippocampi of AD

patients exhibit insulin resistance, whereas moderate alcohol consumption improves insulin sensitivity (Beydoun MA. et al., 2014; Kiechl S. et al., 1996)

9.6 Caffeine

Caffeine is a purine alkaloid in coffee, cola and coca. Caffeine consumption of up to 400 mg per day is considered acceptable for healthy individuals, according to the European Food Safety Authority (EFSA).

This type of study shows varying results. Due to the psychomotor stimulant activity of caffeine, the disruptive effect has been shown on sleep by increasing the arousing effect. The reduction of sleep due to the awakening can decrease memory retention by increasing external stimuli (Londzin P. et al., 2021). In a much larger investigation of 398,646 UK Biobank subjects aged 37 to 73, high daily coffee consumption was associated with gray matter atrophy and dementia risk. Those who drank more than six cups of coffee per day were 53 per cent more likely to develop dementia compared to those who drank only one or two cups per day (Pham K. et al., 2021).

However, various study suggests that caffeine consumption may use in the prophylactic treatment of AD to reduce the risk. In AD, transgenic mice with caffeinated coffee raise granulocyte-colony stimulating factor (GCSF), which is a blood growth factor that improves cognitive performance, enhances synaptogenesis, increases neurogenesis, and increases the number of bone marrow cells (Cao C. et al., 2011). The long-term consumption of caffeine in the animal model also showed a positive effect that increased both the level of cerebrospinal fluid (CSF) and cerebral blood flow production. Both the production and rotation cycle of CSF is involved in the beta-amyloid clearance, which can decrease AD pathogenesis (Wostyn P. et al., 2011).

10. POTENTIAL THERAPIES FOR ALZHEIMER'S

10.1 Evidence-based medication

All four available Alzheimer's disease treatments, including cholinesterase inhibitors and memantine, were accepted more than ten years ago. Acetylcholine (ACh), the messenger between nerve cells, is produced by cholinergic neurons, whose loss is linked to AD. No current AD treatment improves cognitive performance or cures the disease but following drugs slow disease progression and may delay symptom onset. Even if these medicines demonstrate some degree of efficacy, it is unclear what effect their low efficacy will have. This is essential knowledge for patients and their loved ones.

Treatments of first-line are acetylcholinesterase inhibitors (AChEi), including rivastigmine, galantamine, and donepezil which are pharmaceuticals that enhance acetylcholine levels by inhibiting the breakdown of the neurotransmitter by enzyme, Acetylcholinesterase (AChE). AChEi has shown efficacy in treating AD by slowing the cognitive deterioration associated with the disease. All of these pharmaceuticals are equally effective. Among these drugs, donepezil is typically recommended due to its favourable safety profile. Any of these medications can be used to initiate treatment. Every patient must be closely monitored for brain abnormalities, gastrointestinal intolerance, and weight loss (Winslow BT. et al., 2011). As stated in the 2015 update to the "Beers Criteria for Potentially Inappropriate Medication Use in Older Adults", patients with a history of syncope should avoid AChEi due to the risk of bradycardia and orthostatic hypotension. Risks and benefits must be considered when treating elderly patients. (American Geriatrics Society, 2015).

Another authorized oral medication is by use of memantine which is called NMDA receptor antagonist that blocks the action of glutamate to slow the progression of moderate to severe AD. Memantine prevents the excitotoxicity glutamate neurotransmitter from binding to its receptors. This protects neurons in the hippocampus from excitotoxicity and death. Combinations of memantine and AChEi can be used to treat advanced Alzheimer's disease. Now commercially available combination therapy with donepezil and memantine show a significant synergy effect compared to a single drug on AD (Massoud F et al., 2010).

10.2 Current studies and potential new agents

As our understanding of the disease's biology has grown, numerous novel potential treatments have been developed and tested.

In 2018, 112 drugs were in phase I, II, or III studies for Alzheimer's disease. Sixty-three per cent were disease-modifying treatments (DMTs) intended to alter the course of AD and improve outcomes as opposed to symptom management. One-fourth of the medications in development are designed to improve cognition, which can result in improved language, memory, reasoning, and judgment; another ten per cent are aimed at alleviating behavioural signs and symptoms, including apathy, agitation, along with sleep problems. There are several obstacles to AD therapy and DMTs. Despite extensive research, the root cause of this complicated illness remains unknown. Although single-entity therapies have been the focus of testing to date, it is anticipated that combinations will be utilized in the future. Rarely can the results of animal studies on experimental medicines be extrapolated to humans, and many of the medications tested either do not work or have undesirable side effects. It is difficult to recruit and retain participants for lengthy drug studies, and bringing a new medicine candidate to market is expensive. Safe and effective treatments for AD patients and their families require new funding strategies.

Tau and beta-amyloid are typical targets for DMTs. Several medications target the secretases responsible for APP's transformation into beta-amyloid (Cummings J. et al., 2018). Beta-secretases is a proteases that cleavage the beta-site amyloid precursor protein (APP) cleaving enzyme, which initiates the deposition of the beta-amyloid plaque. Both beta- and gamma-secretase are involved in the cleavage of the APP. The beta-secretase activating enzyme (BACE) cleaves APP in addition to a number of other essential brain proteins, leading to amyloid deposition (Armbrust F. et al., 2022). Unlike beta-secretase (BACE), gamma-secretase is an intramembrane protease which is responsible for targeting the whole second phase (Coric V. et al., 2012). BACE inhibitors are effective at reducing the production of beta-amyloid plaques, but they do not reverse plaques or enhance cognitive function (Peters F. et al., 2018). To be effective, these medications must be administered before the majority of AD patients are diagnosed, which can be used as prophylactic. However, Gamma-secretase modulators

(inhibitor) only blocks the gamma-secretase that stop the deposition of the beta-amyloid in the brain, which can be considered as AD therapeutic agent (Kumar D. et al., 2018). As tau protein is associated with neurofibrillary tangles, it is increasingly the target of disease-modifying drugs. Early research in this field centred on the reduction of tau aggregation, but the results were disappointing. These studies did not resolve every issue, but they did inspire the development of seven novel methods for testing tau immunotherapies in phase I and phase II clinical trials.

Numerous medications being studied for their potential to relieve AD-related behavioural symptoms are already commercially available and widely employed to treat a variety of other conditions. When a drug is repurposed from preclinical research to phase II clinical trials, the time it takes to make its way through the drug pipeline may be reduced by half. A few illustrations are antidepressants like escitalopram and mirtazapine, anticonvulsants such as carbamazepine and levetiracetam, mood stabilizers such as lithium, and stimulants such as methylphenidate (Cummings J. et al., 2018).

10.3 Ketogenic diet

Carbohydrate contains high glucose which is the main energy of the brain. A high carbohydrate diet can boost blood sugar levels that increase the risk of AD which can cause damage to blood vessels. Blood vessel impairment can cause ischemia or strokes in the brain that leads to AD. Further, excessive blood levels also destroy glucose and insulin metabolism in elderly, leading to insulin resistance which is also a risk factor for AD (Roberts RO. et al., 2012).

In contrast to glucose, ketone is another fuel of the brain that can boost brain energy. As neurons age, they become less efficient at metabolizing glucose, and scientists have discovered that fat may be able to serve as a substitute fuel source. Further, deposition of beta-amyloid damages mitochondria which is the cells' metabolic source. This damage weakens SIRT3 protein (sirtuin 3). However, the researchers came up with the conclusion that ketones may aid brain health in individuals with early-stage AD as a result of the fact that the rise in SIRT3 levels was associated with the ketones (Cheng A. et al., 2020).

The ketogenic diet is the basics of keto, relating to very low carbohydrates and high fat that force to use of different types of fuel. According to some research, a ketogenic diet produces ketone bodies via the synthesis in the body which has a neuroprotective impact on aging brain cells and reduces inflammatory mediator that enhances cognitive abilities and lessens the risk of developing AD (Rusek M et al.,2019).

The majority of ketogenic diets consist of 70–80% fat, 10–20% protein, and 5–10% carbohydrates. This corresponds to 165 grams of fat, 40 grams of carbohydrates, and 75 grams of protein per 2,000 calories. To use another source of fuel in the body like keto, need to exclude a high carbohydrate diet such as fruits, starchy vegetables (such as potatoes, corn, and peas), legumes, and grains. Avocados, almonds, eggs, cruciferous vegetables, cheeses, and meats are safe to consume. A ketogenic diet will help your body burn excess fat so that you can lose weight (Sullivan MG, 2021).

10.4 MIND diet

MIND diet is a brain-healthy diet that is the combination of both DASH (dietary approaches to stopping hypertension) and Mediterranean diet that can repair the negative effects of obesity on cognitive ability and structures of the brain (Liu X. et al., 2021). This diet increase brain energy that consists of 33% fat, 38% carbohydrates, and 26% protein (Sullivan MG, 2021). For instance, vegetables (green vegetables), berries, extra virgin olive oil, nuts, whole grain and low-fat diet are associatid (Liu X. et al., 2021). In the research, the MIND diet lowered AD risk for about 35% who followed moderate diet rules and up to 53% who adhered strictly (Morris MC et al., 2015).

11. CONCLUSION

There has been and continues to be a substantial amount of research devoted to elucidating the nuances of AD pathophysiology. AD causes, links to other disorders, and preventative measures are still under investigation. However, unless effective therapies and preventative measures are developed, AD will continue to be a significant problem for the ageing population, particularly in Western Europe. If the role of bioactive food consumption in preventing or delaying AD is validated, dietary intervention may be viewed as a viable method for reducing the prevalence of Alzheimer's disease (Celik E. et al.,2019)

12. REFERENCES

1. A Armstrong R. Risk factors for Alzheimer's disease. *Folia Neuropathol.* 2019;57(2):87-105.
2. Abner E. L., Nelson P. T., Jicha G. A., Fardo D. W., Schmitt F. A., Kryscio R. J. Cigarette smoking and risk of dementia in a Kentucky cohort: a competing risk analysis. *Alzheimers Dement.* 2018; 14:973.
3. Acin-Perez R, Hoyos B, Zhao F, et al. Control of oxidative phosphorylation by vitamin A illuminates a fundamental role in mitochondrial energy homeostasis. *FASEB J.* 2010;24(2):627-636.
4. Allen HB. Alzheimer's Disease: Assessing the Role of Spirochetes, Biofilms, the Immune System, and Amyloid- β with Regard to Potential Treatment and Prevention. *J Alzheimers Dis.* 2016;53(4):1271-1276.
5. Alzheimer's Disease. In: Barnard NDN, ed. *Nutrition Guide for Clinicians*. Physicians Committee for Responsible Medicine [online]; 2021, Available from: https://nutritionguide.pcrm.org/nutritionguide/view/Nutrition_Guide_for_Clinicians/1342006/all/Alzheimer's_Disease. Accessed August 28, 2022.
6. American Geriatrics Society 2015 Updated Beers Criteria Expert Panel. American Geriatrics Society 2015 updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults. *J Am Geriatr Soc.* 2015;63(11):2227-2246.
7. Arnoldussen IA, Kiliaan AJ, Gustafson DR. Obesity and dementia: adipokines interact with the brain. *Eur Neuropsychopharmacol.* 2014;24(12):1982-1999.
8. Askarova S, Umbayev B, Masoud AR, et al. The Links Between the Gut Microbiome, Aging, Modern Lifestyle and Alzheimer's Disease. *Front Cell Infect Microbiol.* 2020;10:104.
9. Astarita G, Jung KM, Berchtold NC, et al. Deficient liver biosynthesis of docosahexaenoic acid correlates with cognitive impairment in Alzheimer's disease. *PLoS One.* 2010;5(9):e12538.
10. Austenaa LM, Carlsen H, Ertesvag A, Alexander G, Blomhoff HK, Blomhoff R. Vitamin A status significantly alters nuclear factor-kappaB activity assessed by in vivo imaging. *FASEB J.* 2004;18(11):1255-1257.

11. Ayton S, Faux NG, Bush AI, et al. Ferritin levels in the cerebrospinal fluid predict Alzheimer's disease outcomes and are regulated by APOE. *Nat Commun*. 2015;6:6760.
12. Beydoun MA, Beydoun HA, Gamaldo AA, et al. Epidemiologic studies of modifiable factors associated with cognition and dementia: systematic review and meta-analysis. *BMC Public Health*. 2014;14:643.
13. Beydoun MA, Beydoun HA, Weiss J, Hossain S, El-Hajj ZW, Zonderman AB. Helicobacter pylori, periodontal pathogens, and their interactive association with incident all-cause and Alzheimer's disease dementia in a large national survey. *Mol Psychiatry*. Nature Publishing Group; 2020;1–16.
14. Bordoni A, Hrelia S, Lorenzini A, et al. Dual influence of aging and vitamin B6 deficiency on delta-6-desaturation of essential fatty acids in rat liver microsomes. *Prostaglandins Leukot Essent Fatty Acids*. 1998;58(6):417-420.
15. Bos I, Vos SJ, Frölich L, et al. The frequency and influence of dementia risk factors in prodromal Alzheimer's disease. *Neurobiol Aging*. 2017;56:33-40.
16. Bottiglieri T. Folate, vitamin B₁₂, and S-adenosylmethionine. *Psychiatr Clin North Am*. 2013;36(1):1-13.
17. Brand-Miller, JC. Glycemic load and chronic disease. *Nutr Rev* 61, 2003. S49–S55.
18. Brodala N, Merricks EP, Bellinger DA, et al. Porphyromonas gingivalis bacteremia induces coronary and aortic atherosclerosis in normocholesterolemic and hypercholesterolemic pigs. *Arterioscler Thromb Vasc Biol*. 2005;25(7):1446-1451.
19. Buell JS, Dawson-Hughes B. Vitamin D and neurocognitive dysfunction: preventing "D"ecline?. *Mol Aspects Med*. 2008;29(6):415-422.
20. Calderón-Ospina CA, Nava-Mesa MO. B Vitamins in the nervous system: Current knowledge of the biochemical modes of action and synergies of thiamine, pyridoxine, and cobalamin. *CNS Neurosci Ther*. 2020;26(1):5-13.
21. Cao C, Wang L, Lin X, et al. Caffeine synergizes with another coffee component to increase plasma GCSF: linkage to cognitive benefits in Alzheimer's mice. *J Alzheimers Dis*. 2011;25(2):323-335.
22. Cai Q, Jeong YY. Mitophagy in Alzheimer's Disease and Other Age-Related Neurodegenerative Diseases. *Cells*. 2020;9(1):150.

23. Celik E, Sanlier N. Effects of nutrient and bioactive food components on Alzheimer's disease and epigenetic. *Crit Rev Food Sci Nutr*. 2019;59(1):102-113.
24. Cheng A, Wang J, Ghena N, et al. SIRT3 Haploinsufficiency Aggravates Loss of GABAergic Interneurons and Neuronal Network Hyperexcitability in an Alzheimer's Disease Model. *J Neurosci*. 2020;40(3):694-709.
25. Cholerton B, Gleason CE, Baker LD, Asthana S. Estrogen and Alzheimer's disease: the story so far. *Drugs Aging*. 2002;19(6):405-427.
26. Coric V, van Dyck CH, Salloway S, et al. Safety and tolerability of the γ -secretase inhibitor avagacestat in a phase 2 study of mild to moderate Alzheimer disease. *Arch Neurol*. 2012;69(11):1430-1440.
27. Cummings J, Lee G, Ritter A, Zhong K. Alzheimer's disease drug development pipeline: 2018. *Alzheimers Dement (N Y)*. 2018;4:195-214.
28. Cutler RG, Kelly J, Storie K, et al. Involvement of oxidative stress-induced abnormalities in ceramide and cholesterol metabolism in brain aging and Alzheimer's disease. *Proc Natl Acad Sci U S A*. 2004;101(7):2070-2075.
29. Dake MD, De Marco M, Blackburn DJ, et al. Obesity and Brain Vulnerability in Normal and Abnormal Aging: A Multimodal MRI Study. *J Alzheimers Dis Rep*. 2021;5(1):65-77.
30. Das BC, Dasgupta S, Ray SK. Potential therapeutic roles of retinoids for prevention of neuroinflammation and neurodegeneration in Alzheimer's disease. *Neural Regen Res*. 2019;14(11):1880-1892.
31. De La Monte SM. Metabolic derangements mediate cognitive impairment and Alzheimer's disease: role of peripheral insulin-resistance diseases. *Panminerva Med*. 2012;54(3):171-178.
32. Desrumaux C, Pisoni A, Meunier J, et al. Increased amyloid- β peptide-induced memory deficits in phospholipid transfer protein (PLTP) gene knockout mice. *Neuropsychopharmacology*. 2013;38(5):817-825.
33. Devore EE, Grodstein F, van Rooij FJ, et al. Dietary antioxidants and long-term risk of dementia. *Arch Neurol*. 2010;67(7):819-825.
34. Devanand DP, Andrews H, Kreisl WC, et al. Antiviral therapy: Valacyclovir Treatment of Alzheimer's Disease (VALAD) Trial: protocol for a randomised, double-blind, placebo-controlled, treatment trial. *BMJ Open*. 2020;10(2):e032112.

35. Dhouafli Z, Cuanalo-Contreras K, Hayouni EA, Mays CE, Soto C, Moreno-Gonzalez I. Inhibition of protein misfolding and aggregation by natural phenolic compounds. *Cell Mol Life Sci.* 2018;75(19):3521-3538.
36. Dietschy JM. Dietary fatty acids and the regulation of plasma low density lipoprotein cholesterol concentrations. *J Nutr.* 1998;128(2 Suppl):444S-448S.
37. Ding Y, Ren J, Yu H, Yu W, Zhou Y. *Porphyromonas gingivalis*, a periodontitis causing bacterium, induces memory impairment and age-dependent neuroinflammation in mice. *Immun Ageing.* 2018;15:6.
38. Dominy SS, Lynch C, Ermini F, et al. *Porphyromonas gingivalis* in Alzheimer's disease brains: Evidence for disease causation and treatment with small-molecule inhibitors. *Sci Adv.* 2019;5(1)
39. Dysken MW, Sano M, Asthana S, et al. Effect of vitamin E and memantine on functional decline in Alzheimer disease: the TEAM-AD VA cooperative randomized trial [published correction appears in JAMA. 2014 Mar 19;311(11):1161]. *JAMA.* 2014;311(1):33-44.
40. Ebrahimi K, Majdi A, Baghaiee B, Hosseini SH, Sadigh-Eteghad S. Physical activity and beta-amyloid pathology in Alzheimer's disease: A sound mind in a sound body. *EXCLI J.* 2017;16:959-972.
41. Edwards GA III, Gamez N, Escobedo G Jr, Calderon O and Moreno-Gonzalez I. Modifiable Risk Factors for Alzheimer's Disease. *Front. Aging Neurosci.* 2019; 11:146.
42. Eimer WA, Vijaya Kumar DK, Navalpur Shanmugam NK, et al. Alzheimer's Disease-Associated β -Amyloid Is Rapidly Seeded by Herpesviridae to Protect against Brain Infection [published correction appears in Neuron. 2018 Dec 19;100(6):1527-1532]. *Neuron.* 2018;99(1):56-63.e3.
43. Erickson KI, Voss MW, Prakash RS, et al. Exercise training increases size of hippocampus and improves memory. *Proc Natl Acad Sci U S A.* 2011;108(7):3017-3022.
44. Fernández-Sanz P, Ruiz-Gabarre D, García-Escudero V. Modulating Effect of Diet on Alzheimer's Disease. *Diseases.* 2019;7(1):12.
45. Armbrust F, Bickenbach K, Marengo L, Pietrzik C, Becker-Pauly C. The Swedish dilemma - the almost exclusive use of APP^{sw}-based mouse models impedes

- adequate evaluation of alternative β -secretases. *Biochim Biophys Acta Mol Cell Res.* 2022;1869(3):119164.
46. Gamba P, Testa G, Gargiulo S, et al. Oxidized cholesterol as the driving force behind the development of Alzheimer's disease. *Front Aging Neurosci.* 2015;7:119.
 47. Gardener SL, Rainey-Smith SR. The Role of Nutrition in Cognitive Function and Brain Ageing in the Elderly. *Curr Nutr Rep.* 2018;7(3):139-149.
 48. Gibson GE, Hirsch JA, Fonzetti P, Jordan BD, Cirio RT, Elder J. Vitamin B1 (thiamine) and dementia. *Ann N Y Acad Sci.* 2016;1367(1):21-30.
 49. Gugliandolo A, Bramanti P, Mazzon E. Role of Vitamin E in the Treatment of Alzheimer's Disease: Evidence from Animal Models. *Int J Mol Sci.* 2017;18(12):2504.
 50. Guyonnet S, Abellan Van Kan G, Andrieu S, et al. IANA task force on nutrition and cognitive decline with aging. *J Nutr Health Aging.* 2007;11(2):132-52.
 51. Grant WB. Using Multicountry Ecological and Observational Studies to Determine Dietary Risk Factors for Alzheimer's Disease. *J Am Coll Nutr.* 2016;35(5):476-89.
 52. Gugliandolo A, Chiricosta L, Silvestro S, Bramanti P, Mazzon E. α -Tocopherol Modulates Non-Amyloidogenic Pathway and Autophagy in an In Vitro Model of Alzheimer's Disease: A Transcriptional Study. *Brain Sci.* 2019;9(8):196.
 53. Harding A, Gonder U, Robinson SJ, Crean S, Singhrao SK. Exploring the Association between Alzheimer's Disease, Oral Health, Microbial Endocrinology and Nutrition. *Front Aging Neurosci.* 2017;9:398.
 54. Harris CJ, Voss K, Murchison C, et al. Oral zinc reduces amyloid burden in Tg2576 mice. *J Alzheimers Dis.* 2014;41(1):179-92.
 55. Harrison FE. A critical review of vitamin C for the prevention of age-related cognitive decline and Alzheimer's disease. *J Alzheimers Dis.* 2012;29(4):711-26.
 56. Hayashi C, Gudino CV, Gibson FC 3rd, Genco CA. Review: Pathogen-induced inflammation at sites distant from oral infection: bacterial persistence and induction of cell-specific innate immune inflammatory pathways. *Mol Oral Microbiol.* 2010;25(5):305-316.
 57. Henderson ST. High carbohydrate diets and Alzheimer's disease. *Med Hypotheses.* 2004;62(5):689-700.

58. Heymann D, Stern Y, Cosentino S, Tatarina-Nulman O, Dorrejo JN, Gu Y. The Association Between Alcohol Use and the Progression of Alzheimer's Disease. *Curr Alzheimer Res.* 2016;13(12):1356-1362.
59. Hildreth KL, Van Pelt RE, Schwartz RS. Obesity, insulin resistance, and Alzheimer's disease. *Obesity (Silver Spring).* 2012;20(8):1549-1557.
60. Hira S, Saleem U, Anwar F, Sohail MF, Raza Z, Ahmad B. β -Carotene: A Natural Compound Improves Cognitive Impairment and Oxidative Stress in a Mouse Model of Streptozotocin-Induced Alzheimer's Disease. *Biomolecules.* 2019;9(9):441.
61. Holth JK, Fritschi SK, Wang C, et al. The sleep-wake cycle regulates brain interstitial fluid tau in mice and CSF tau in humans. *Science.* 2019;363(6429):880-884.
62. Horrocks LA, Farooqui AA. Docosahexaenoic acid in the diet: its importance in maintenance and restoration of neural membrane function. *Prostaglandins Leukot Essent Fatty Acids.* 2004;70(4):361-372.
63. Hsu TM, Kanoski SE. Blood-brain barrier disruption: mechanistic links between Western diet consumption and dementia. *Front Aging Neurosci.* 2014;6:88.
64. Huat TJ, Camats-Perna J, Newcombe EA, Valmas N, Kitazawa M, Medeiros R. Metal Toxicity Links to Alzheimer's Disease and Neuroinflammation. *J Mol Biol.* 2019;431(9):1843-1868.
65. Husson M, Enderlin V, Delacourte A, et al. Retinoic acid normalizes nuclear receptor mediated hypo-expression of proteins involved in beta-amyloid deposits in the cerebral cortex of vitamin A deprived rats. *Neurobiol Dis* 23, 2006; 1–10.
66. Ilievski V, Zuchowska PK, Green SJ, Toth PT, Ragozzino ME, et al. Chronic oral application of a periodontal pathogen results in brain inflammation, neurodegeneration and amyloid beta production in wild type mice. *PLOS ONE* 2018; 13(10)
67. Ishida N, Ishihara Y, Ishida K, et al. Periodontitis induced by bacterial infection exacerbates features of Alzheimer's disease in transgenic mice. *NPJ Aging Mech Dis.* 2017;3:15.
68. Ising C, Stanley M, Holtzman DM. Current thinking on the mechanistic basis of Alzheimer's and implications for drug development. *Clin Pharmacol Ther.* 2015;98(5):469-471.

69. Jayasooriya AP, Ackland ML, Mathai ML, et al. Perinatal omega-3 polyunsaturated fatty acid supply modifies brain zinc homeostasis during adulthood [published correction appears in *Proc Natl Acad Sci U S A*. 2005 Aug 2;102(31):11124]. *Proc Natl Acad Sci U S A*. 2005;102(20):7133-7138.
70. Jiménez-Jiménez FJ, de Bustos F, Molina JA, et al. Cerebrospinal fluid levels of alpha-tocopherol in patients with multiple sclerosis. *Neurosci Lett*. 1998;249(1):65-67.
71. Jung HY, Kim DW, Nam SM, et al. Pyridoxine improves hippocampal cognitive function via increases of serotonin turnover and tyrosine hydroxylase, and its association with CB1 cannabinoid receptor-interacting protein and the CB1 cannabinoid receptor pathway. *Biochim Biophys Acta Gen Subj*. 2017;1861(12):3142-3153.
72. Kamer AR, Craig RG, Pirraglia E, et al. TNF-alpha and antibodies to periodontal bacteria discriminate between Alzheimer's disease patients and normal subjects. *J Neuroimmunol*. 2009;216(1-2):92-97.
73. Kellar D, Craft S. Brain insulin resistance in Alzheimer's disease and related disorders: mechanisms and therapeutic approaches. *Lancet Neurol*. 2020;19(9):758-766.
74. Kennedy DO. B Vitamins and the Brain: Mechanisms, Dose and Efficacy--A Review. *Nutrients*. 2016;8(2):68.
75. Kennedy MS, Chang EB. The microbiome: Composition and locations. *Prog Mol Biol Transl Sci*. 2020;176:1-42.
76. Khan SA, Vanden Heuvel JP. Role of nuclear receptors in the regulation of gene expression by dietary fatty acids (review). *J Nutr Biochem*. 2003;14(10):554-567.
77. Kiechl S, Willeit J, Poewe W, Egger G, Oberhollenzer F, Muggeo M et al. Insulin sensitivity and regular alcohol consumption: large, prospective, cross sectional population study (Bruneck study) *BMJ* 1996; 313 :1040 -
78. Kiliaan AJ, Arnoldussen IA, Gustafson DR. Adipokines: a link between obesity and dementia?. *Lancet Neurol*. 2014;13(9):913-923
79. Kim YK, Hammerling U. The mitochondrial PKC δ /retinol signal complex exerts real-time control on energy homeostasis. *Biochim Biophys Acta Mol Cell Biol Lipids*. 2020;1865(11):158614.

80. Kinuta K, Tanaka H, Moriwake T, Aya K, Kato S, Seino Y. Vitamin D is an important factor in estrogen biosynthesis of both female and male gonads. *Endocrinology*. 2000;141(4):1317-1324.
81. Kok N, Roberfroid M, Delzenne N. Dietary oligofructose modifies the impact of fructose on hepatic triacylglycerol metabolism. *Metabolism*. 1996;45(12):1547-1550.
82. Kook SY, Lee KM, Kim Y, et al. High-dose of vitamin C supplementation reduces amyloid plaque burden and ameliorates pathological changes in the brain of 5XFAD mice. *Cell Death Dis*. 2014;5(2):e1083.
83. Kou J, Kovacs GG, Höftberger R, et al. Peroxisomal alterations in Alzheimer's disease. *Acta Neuropathol*. 2011;122(3):271-283.
84. Kowalski K, Mulak A. Brain-Gut-Microbiota Axis in Alzheimer's Disease. *J Neurogastroenterol Motil*. 2019;25(1):48-60.
85. Kumar D, Ganeshpurkar A, Kumar D, et al. Secretase inhibitors for the treatment of Alzheimer's disease: long road ahead. *Eur J Med Chem*. 2018;148:436-452.
86. Landel V, Annweiler C, Millet P, Morello M, Féron F. Vitamin D, Cognition and Alzheimer's Disease: The Therapeutic Benefit is in the D-Tails. *J Alzheimers Dis*. 2016;53(2):419-444.
87. Langlais PJ. Alcohol-Related Thiamine Deficiency: Impact on Cognitive and Memory Functioning. *Alcohol Health Res World*. 1995;19(2):113-121.
88. Lauer AA, Grimm HS, Apel B, et al. Mechanistic Link between Vitamin B12 and Alzheimer's Disease. *Biomolecules*. 2022;12(1):129.
89. Leblhuber F, Huemer J, Steiner K, Gostner JM, Fuchs D. Knock-on effect of periodontitis to the pathogenesis of Alzheimer's disease? [published correction appears in *Wien Klin Wochenschr*. 2020 Apr 6;:]. *Wien Klin Wochenschr*. 2020;132(17-18):493-498.
90. Levine M, Wang Y, Padayatty SJ, Morrow J. A new recommended dietary allowance of vitamin C for healthy young women. *Proc Natl Acad Sci U S A*. 2001;98(17):9842-9846.
91. Lim GP, Calon F, Morihara T, Yang F, Teter B, Ubeda O *et al*. A diet enriched with the omega-3 fatty acid docosahexaenoic acid reduces amyloid burden in an aged Alzheimer mouse model. *J Neurosci* 2005; 25: 3032–3040.

92. Lim MM, Gerstner JR, Holtzman DM. The sleep-wake cycle and Alzheimer's disease: what do we know?. *Neurodegener Dis Manag*. 2014;4(5):351-362.
93. Liu JL, Fan YG, Yang ZS, Wang ZY, Guo C. Iron and Alzheimer's Disease: From Pathogenesis to Therapeutic Implications. *Front Neurosci*. 2018;12:632.
94. Liu X, Morris MC, Dhana K, et al. Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) study: Rationale, design and baseline characteristics of a randomized control trial of the MIND diet on cognitive decline. *Contemp Clin Trials*. 2021;102:106270.
95. Liu XY, Yang LP, Zhao L. Stem cell therapy for Alzheimer's disease. *World J Stem Cells*. 2020;12(8):787-802.
96. Loef M, von Stillfried N, Walach H. Zinc diet and Alzheimer's disease: a systematic review. *Nutr Neurosci*. 2012;15(5):2-12.
97. Londzin P, Zamora M, Kałkol B, Taborek A, Folwarczna J. Potential of Caffeine in Alzheimer's Disease-A Review of Experimental Studies. *Nutrients*. 2021;13(2):537
98. López-García S, Lage C, Pozueta A, García-Martínez M, Kazimierczak M, Fernández-Rodríguez A, Bravo M, Reyes-González L, Irure J, López-Hoyos M, Rodríguez-Rodríguez E and Sánchez-Juan P. Sleep Time Estimated by an Actigraphy Watch Correlates With CSF Tau in Cognitively Unimpaired Elders: The Modulatory Role of APOE. *Front. Aging Neurosci*. 2021; 13:663446.
99. Lorenzo M, Refolo, Miguel A, Pappolla, Brian Malester, John LaFrancois, Tara Bryant-Thomas, Rong Wang, G.Stephen Tint, Kumar Sambamurti, Karen Duff, Hypercholesterolemia Accelerates the Alzheimer's Amyloid Pathology in a Transgenic Mouse Model, *Neurobiology of Disease*, Volume 7, Issue 4, 2000; 321-331
100. Lu Y, Dong Y, Tucker D, et al. Treadmill Exercise Exerts Neuroprotection and Regulates Microglial Polarization and Oxidative Stress in a Streptozotocin-Induced Rat Model of Sporadic Alzheimer's Disease. *J Alzheimers Dis*. 2017;56(4):1469-1484.
101. Lukiw WJ. *Bacteroides fragilis* Lipopolysaccharide and Inflammatory Signaling in Alzheimer's Disease. *Front Microbiol*. 2016;7:1544.
102. Malouf R, Grimley Evans J. The effect of vitamin B6 on cognition. *Cochrane Database Syst Rev*. 2003;(4):CD004393.
103. Marino LV, Ramos LF, Chiarello PG. Nutritional status according to the stages of Alzheimer's disease. *Aging Clin Exp Res*. 2015;27(4):507-513.

104. Massaad CA, Pautler RG, Klann E. Mitochondrial superoxide: a key player in Alzheimer's disease. *Aging (Albany NY)*. 2009;1(9):758-761.
105. Massoud F, Gauthier S. Update on the pharmacological treatment of Alzheimer's disease. *Curr Neuropharmacol*. 2010;8(1):69-80.
106. Metz J. Cobalamin deficiency and the pathogenesis of nervous system disease. *Annu Rev Nutr*. 1992;12:59-79.
107. Michaelson DM. APOE ϵ 4: the most prevalent yet understudied risk factor for Alzheimer's disease. *Alzheimers Dement*. 2014;10(6):861-868.
108. Mielech A, Puścion-Jakubik A, Markiewicz-Żukowska R, Socha K. Vitamins in Alzheimer's Disease-Review of the Latest Reports. *Nutrients*. 2020;12(11):3458.
109. Mielke MM, Bandaru VV, Haughey NJ, et al. Serum ceramides increase the risk of Alzheimer disease: the Women's Health and Aging Study II. *Neurology*. 2012;79(7):633-641.
110. Miklossy J. Alzheimer's disease - a neurospirochetosis. Analysis of the evidence following Koch's and Hill's criteria. *J Neuroinflammation*. 2011;8:90.
111. Miklossy J. Historic evidence to support a causal relationship between spirochetal infections and Alzheimer's disease. *Front Aging Neurosci*. 2015;7:46.
112. Miller AL. The methionine-homocysteine cycle and its effects on cognitive diseases. *Altern Med Rev*. 2003;8(1):7-19.
113. Morris MC. Diet and Alzheimer's disease: what the evidence shows. *MedGenMed*. 2004;6(1):48
114. Morris MC, Evans DA, Bienias JL, et al. Dietary intake of antioxidant nutrients and the risk of incident Alzheimer disease in a biracial community study. *JAMA*. 2002;287(24):3230-7.
115. Morris, MC, Evans, DA, Bienias, JL, et al. Dietary niacin and the risk of incident Alzheimer's disease and of cognitive decline. *J Neurol Neurosurg Psychiatry* 75, 2004; 1093–1099.
116. Morris MC, Schneider JA, Li H, et al. Brain tocopherols related to Alzheimer's disease neuropathology in humans. *Alzheimers Dement*. 2015;11(1):32-39
117. Morris MC, Tangney CC. Dietary fat composition and dementia risk. *Neurobiol Aging*. 2014;35 Suppl 2:S59-64.

118. Morris MC, Tangney CC, Wang Y, Sacks FM, Bennett DA, Aggarwal NT. MIND diet associated with reduced incidence of Alzheimer's disease. *Alzheimers Dement.* 2015;11(9):1007-1014.
119. Obeid R, Herrmann W. Mechanisms of homocysteine neurotoxicity in neurodegenerative diseases with special reference to dementia. *FEBS Lett.* 2006;580(13):2994-3005.
120. Oliveros LB, Domeniconi MA, Vega VA, Gatica LV, Brigada AM, Gimenez MS. Vitamin A deficiency modifies lipid metabolism in rat liver. *Br J Nutr.* 2007;97(2):263-272.
121. Olsen I, Singhrao SK. Can oral infection be a risk factor for Alzheimer's disease?. *J Oral Microbiol.* 2015;7:29143.
122. Parady B. Innate Immune and Fungal Model of Alzheimer's Disease. *J Alzheimers Dis Rep.* 2018;2(1):139-152
123. Parker A, James SA, Purse C, et al. Absence of Bacteria Permits Fungal Gut-To-Brain Translocation and Invasion in Germfree Mice but Ageing Alone Does Not Drive Pathobiont Expansion in Conventionally Raised Mice. *Front Aging Neurosci.* 2022;14:828429.
124. Peng Y, Chang X, Lang M. Iron Homeostasis Disorder and Alzheimer's Disease. *Int J Mol Sci.* 2021;22(22):12442.
125. Peron R, Vatanabe IP, Manzine PR, Camins A, Cominetti MR. Alpha-Secretase ADAM10 Regulation: Insights into Alzheimer's Disease Treatment. *Pharmaceuticals.* 2018; 11(1):12.
126. Peters DG, Connor JR, Meadowcroft MD. The relationship between iron dyshomeostasis and amyloidogenesis in Alzheimer's disease: Two sides of the same coin. *Neurobiol Dis.* 2015;81:49-65.
127. Peters F, Salihoglu H, Rodrigues E, et al. BACE1 inhibition more effectively suppresses initiation than progression of β -amyloid pathology. *Acta Neuropathol.* 2018;135(5):695-710.
128. Pham K, Mulugeta A, Zhou A, O'Brien JT, Llewellyn DJ, Hyppönen E. High coffee consumption, brain volume and risk of dementia and stroke [published online ahead of print, 2021 Jun 24]. *Nutr Neurosci.* 2021;1-12.

129. Pitkälä KH, Pöysti MM, Laakkonen M, et al. Effects of the Finnish Alzheimer Disease Exercise Trial (FINALEX): A Randomized Controlled Trial. *JAMA Intern Med.* 2013;173(10):894–901.
 130. Prescott SL. History of medicine: origin of the term microbiome and why it matters. *Hum Microbiome J.* 2017;4:24–25.
 131. Pruccoli J, Parmeggiani A, Cordelli DM, Lanari M. The Role of the Noradrenergic System in Eating Disorders: A Systematic Review. *Int J Mol Sci.* 2021;22(20):11086.
 132. Reddy OC, van der Werf YD. The Sleeping Brain: Harnessing the Power of the Glymphatic System through Lifestyle Choices. *Brain Sci.* 2020;10(11):868.
 133. Reginato A, Veras ACC, Baqueiro MDN, et al. The Role of Fatty Acids in Ceramide Pathways and Their Influence on Hypothalamic Regulation of Energy Balance: A Systematic Review. *Int J Mol Sci.* 2021;22(10):5357.
 134. Rehm J, Gmel G, Sempos CT, et al. Alcohol-related morbidity and mortality. *Alcohol Res Health.* 2003;27(1):39-51.
 135. Rehm J. The risks associated with alcohol use and alcoholism. *Alcohol Res. Health* 34, 2011; 135–143.
 136. Ries M, Sastre M. Mechanisms of A β Clearance and Degradation by Glial Cells. *Front Aging Neurosci.* 2016;8:160.
 137. Rivers-Auty J, Tapia VS, White CS, et al. Zinc Status Alters Alzheimer's Disease Progression through NLRP3-Dependent Inflammation. *J Neurosci.* 2021;41(13):3025-3038.
- Roberts RO, Roberts LA, Geda YE, et al. Relative intake of macronutrients impacts risk of mild cognitive impairment or dementia. *J Alzheimers Dis.* 2012;32(2):329-339
138. Rogaev EI, Lukiw WJ, Lavrushina O, Rogaeva EA, St George-Hyslop PH. The upstream promoter of the beta-amyloid precursor protein gene (APP) shows differential patterns of methylation in human brain. *Genomics.* 1994;22(2):340-347.
 139. Roh JH, Jiang H, Finn MB, et al. Potential role of orexin and sleep modulation in the pathogenesis of Alzheimer's disease [published correction appears in *J Exp Med.* 2015 Jan 12;212(1):121]. *J Exp Med.* 2014;211(13):2487-2496.
 140. Rusek M, Pluta R, Ułamek-Kozioł M, Czuczwar SJ. Ketogenic Diet in Alzheimer's Disease. *Int J Mol Sci.* 2019;20(16):3892.

141. Sambra V, Echeverria F, Valenzuela A, Chouinard-Watkins R, Valenzuela R. Docosahexaenoic and Arachidonic Acids as Neuroprotective Nutrients throughout the Life Cycle. *Nutrients*. 2021;13(3):986.
142. Sato Y, Asoh T, Oizumi K. High prevalence of vitamin D deficiency and reduced bone mass in elderly women with Alzheimer's disease [retracted in: Bone. 2019 Aug;125:210]. *Bone*. 1998;23(6):555-557.
143. Schmukler, E., Michaelson, D.M. & Pinkas-Kramarski, R. The Interplay Between Apolipoprotein E4 and the Autophagic-Endocytic-Lysosomal Axis. *Mol Neurobiol* 55, 2018; 6863-6880
144. Schrag M, Mueller C, Oyoyo U, Smith MA, Kirsch WM. Iron, zinc and copper in the Alzheimer's disease brain: a quantitative meta-analysis. Some insight on the influence of citation bias on scientific opinion. *Prog Neurobiol*. 2011;94(3):296-306.
145. Seshadri S, Beiser A, Selhub J, et al. Plasma homocysteine as a risk factor for dementia and Alzheimer's disease. *N Engl J Med*. 2002;346(7):476-83.
146. Shen L, Ji HF. Vitamin D deficiency is associated with increased risk of Alzheimer's disease and dementia: evidence from meta-analysis. *Nutr J*. 2015;14:76.
147. Shukla M, Govitrapong P, Boontem P, Reiter RJ, Satayavivad J. Mechanisms of Melatonin in Alleviating Alzheimer's Disease. *Curr Neuropharmacol*. 2017;15(7):1010-1031.
148. Silva I, Silva J, Ferreira R, Trigo D. Glymphatic system, AQP4, and their implications in Alzheimer's disease. *Neurol Res Pract*. 2021;3(1):5.
149. Singleton CK, Martin PR. Molecular mechanisms of thiamine utilization. *Curr Mol Med*. 2001;1(2):197-207.
150. Smith TJ, Johnson CR, Koshy R, et al. Thiamine deficiency disorders: a clinical perspective. *Ann N Y Acad Sci*. 2021;1498(1):9-28.
151. Sparks Stein P, Steffen MJ, Smith C, et al. Serum antibodies to periodontal pathogens are a risk factor for Alzheimer's disease. *Alzheimers Dement*. 2012;8(3):196-203.
152. Squitti R, Siotto M, Polimanti R. Low-copper diet as a preventive strategy for Alzheimer's disease. *Neurobiol Aging*. 2014;35 Suppl 2:S40-50.
153. Sullivan, Michele G. "Could Keto Diets Offer Brain Health Benefits?" AARP [online] 2021. Available from: <https://www.aarp.org/health/dementia/info->

2021/keto-diet-

alzheimers.html#:~:text=The%20newest%20science%20suggests%20that,disorder%20in%20the%20first%20place.

154. Swaminathan A, Jicha GA. Nutrition and prevention of Alzheimer's dementia. *Front Aging Neurosci.* 2014;6:282.
155. Honda T, Ohara T, Shinohara M, et al. Serum elaidic acid concentration and risk of dementia: The Hisayama Study. *Neurology.* 2019;93(22):e2053-e2064.
156. Tajmim A, Cuevas-Ocampo AK, Siddique AB, et al. (-)-Oleocanthal Nutraceuticals for Alzheimer's Disease Amyloid Pathology: Novel Oral Formulations, Therapeutic, and Molecular Insights in 5xFAD Transgenic Mice Model. *Nutrients.* 2021;13(5):1702.
157. Travica N, Ried K, Sali A, Scholey A, Hudson I, Pipingas A. Vitamin C Status and Cognitive Function: A Systematic Review. *Nutrients.* 2017;9(9):960.
158. Tseng BY, Uh J, Rossetti HC, et al. Masters athletes exhibit larger regional brain volume and better cognitive performance than sedentary older adults. *J Magn Reson Imaging.* 2013;38(5):1169-1176.
159. Udhayabanu T, Manole A, Rajeshwari M, Varalakshmi P, Houlden H, Ashokkumar B. Riboflavin Responsive Mitochondrial Dysfunction in Neurodegenerative Diseases. *J Clin Med.* 2017;6(5):52.
160. Umhau JC, Dauphinais KM, Patel SH, et al. The relationship between folate and docosahexaenoic acid in men. *Eur J Clin Nutr.* 2006;60(3):352-357.
161. Ursell LK, Metcalf JL, Parfrey LW, Knight R. Defining the human microbiome. *Nutr Rev.* 2012;70(Suppl 1):S38–S44.
162. Ventriglia M, Bucossi S, Panetta V, Squitti R. Copper in Alzheimer's disease: a meta-analysis of serum, plasma, and cerebrospinal fluid studies. *J Alzheimers Dis.* 2012;30(4):981-984.
163. Vinogradova Y, Denning T, Hippisley Cox J, Taylor L, Moore M, Coupland C et al. Use of menopausal hormone therapy and risk of dementia: nested case-control studies using QResearch and CPRD databases *BMJ* 2021; 374:n2182
164. Wakimoto, P & Block, G. Dietary intake, dietary patterns, and changes with age: an epidemiological perspective. *J Gerontol A Biol Sci Med Sci* 56, 2001. 65–80.

165. Wang Y, Shi Y, Wei H. Calcium Dysregulation in Alzheimer's Disease: A Target for New Drug Development. *J Alzheimers Dis Parkinsonism*. 2017;7(5):374.
166. Whitmer RA, Gunderson EP, Barrett-Connor E, Quesenberry CP Jr, Yaffe K. Obesity in middle age and future risk of dementia: a 27 year longitudinal population based study. *BMJ*. 2005;330(7504):1360.
167. Winslow BT, Onysko MK, Stob CM, Hazlewood KA. Treatment of Alzheimer disease. *Am Fam Physician*. 2011;83(12):1403-1412.
168. Wójtowicz S, Strosznajder AK, Jeżyna M, Strosznajder JB. The Novel Role of PPAR Alpha in the Brain: Promising Target in Therapy of Alzheimer's Disease and Other Neurodegenerative Disorders. *Neurochem Res*. 2020;45(5):972-988.
169. World Health Organization. *WHO Report on the Global Tobacco Epidemic. Enforcing Bans on Tobacco Advertising, Promotion and Sponsorship Fresh and Alive Mpower. Includes A Special Section on Five Years of Progress*. Geneva: World Health Organization. 2013.
170. Wostyn P, Van Dam D, Audenaert K, De Deyn PP. Increased Cerebrospinal Fluid Production as a Possible Mechanism Underlying Caffeine's Protective Effect against Alzheimer's Disease. *Int J Alzheimers Dis*. 2011;2011:617420.
171. Wozniak MA, Itzhaki RF, Shipley SJ, Dobson CB. Herpes simplex virus infection causes cellular beta-amyloid accumulation and secretase upregulation. *Neurosci Lett*. 2007;429(2-3):95-100.
172. Yatin SM, Varadarajan S, Butterfield DA. Vitamin E Prevents Alzheimer's Amyloid beta-Peptide (1-42)-Induced Neuronal Protein Oxidation and Reactive Oxygen Species Production. *J Alzheimers Dis*. 2000;2(2):123-131.
173. Yiannopoulou KG, Papageorgiou SG. Current and Future Treatments in Alzheimer Disease: An Update. *J Cent Nerv Syst Dis*. 2020;12:1179573520907397
174. Zeng J, Chen L, Wang Z, et al. Marginal vitamin A deficiency facilitates Alzheimer's pathogenesis. *Acta Neuropathol*. 2017;133(6):967-982.
175. Zhang T, Han X, Zhang X, Chen Z, Mi Y, Gou X. Dietary Fatty Acid Factors in Alzheimer's Disease: A Review. *J Alzheimers Dis*. 2020;78(3):887-904.
176. Zhao Y, Dong X, Chen B, Zhang Y, Meng S, Guo F, Guo X, Zhu J, Wang H, Cui H and Li S Blood levels of circulating methionine components in Alzheimer's disease

and mild cognitive impairment: A systematic review and meta-analysis. *Front. Aging Neurosci.* 2022; 14:934070.

177. Zieger E, Schubert M. New Insights Into the Roles of Retinoic Acid Signaling in Nervous System Development and the Establishment of Neurotransmitter Systems. *Int Rev Cell Mol Biol.* 2017;330:1-84.