Investigating the Mediterranean diet's role in Alzheimer's disease prevention: A review

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Abstract. Alzheimer's disease (AD) is the most common type of dementia, and it is a neurological ailment that worsens with time with no known cure. AD research is paying more and more attention to lifestyle factors, including diet and nutrition. The Mediterranean diet (MeDi) may offer defence against dementia and cognitive deterioration, according to some research. According to various epidemiological studies, people who follow a MeDi have a lower risk of developing cognitive problems. Higher MeDi adherence was linked to a lower likelihood of incident cognitive impairment, whereas lower adherence was linked to a rise in AD and mild cognitive impairment. Progressive AD biomarker abnormalities have been linked to lower MeDi adherence in middle-aged adults. Reduced vascular risk factors and favourable effects on glucose and lipid metabolism may also contribute to the MeDi's lower risk of AD. The MeDi may have preventive effects against cognitive decline, including AD, because to some of its components, including its high fruit and vegetable content, relatively low level of carbs, and usage of added-virgin olive oil as the primary basis of fat. However, other aspects of the Mediterranean lifestyle, such consistent exercise and robust social networks, might help lower the risk of the illness. To prove a link between MeDi and the prevention or amelioration of cognitive loss in AD, long-term randomised controlled trials are required. Since it is unknown what specific food components and bioactives are needed for efficient neuroprotection, it is currently not practical to prescribe the MeDi as a preventive measure in AD. According to the available evidence, the MeDi should be implemented as part of public health initiatives aimed at lowering the risk of AD.

Key words: Alzheimer disease, Mediterranean diet, bioactive compounds, neurodegeneration, nutriepigenomics

Introduction

The two-neurodegenerative illnesses with the highest prevalence are Alzheimer's disease (AD) and Parkinson's disease (PD). According to Hebert et al. (2013) and Marras et al. (2018), 9.4 million Americans will be diagnosed with PD (1.2 million) or AD (8.2 million) by 2030 (1, 2). For both people and society, AD and PD represent a significant burden. Since there are no cures for AD or PD, attention should be given to prevention measures including changing one's diet and other modifiable lifestyle variables.

Due to its low fibre content, the Western diet may contribute to AD or PD (3, 4). In comparison to the western diet, Mediterranean diet (MeDi) contains lot of fibre. The positive impacts of attached to the MeDi could be facilitated by the gut microbial makeup because fibre is a primary energy substrate for gut flora. As dysbiosis, an disparity in the microbial ecology, has been hypothesised as a tool for neuroinflammation

heading to PD or AD, maintaining a eubiotic gut conditions may be vital for healthy brain ageing (5). Previous studies suggested that MeDi may have a protective effect on the neurodegenerative disorders such as AD and PD (6, 7). The diet is rich in antioxidants, fiber, and omega-3 polyunsaturated fatty acids and many more nutrients. Natural products have recently undergone extensive exploration and study for their therapeutic ability for different diseases are because of the presence of bioactive compounds. The diet could prevent cell death and restore function to damaged neurons by targeting multiple mechanisms of action. For these reasons, the therapeutic potential of natural products and the connections between the MeDi and neurodegenerative diseases have recently been studied in cross sectional as well as longitudinal study design (8-10). As a result, the study aims to compile the most recent findings to provide readers with an overview of the potential advantages of bioactive compounds found in the MeDi, as well as information about their origin and potential mechanisms of action in neurodegenerative diseases.

Mediterranean diet, brain, and muscle

Due to its prominent consumption of almonds, olive oil, legumes, red wine, vegetables, and fruits—all key foods that are rich in antioxidants and polyphenols—the MeDi is widely regarded as a great nutritional model. Numerous phytochemicals and synthetic compounds including polyphenols by demonstrated health benefits exhibit qualities that are beneficial to human health (11).

The notion that a balanced diet could be extremely important in supporting health is now firmly established. The MeDi is a good example of a dietary outline that is distinguished by a high intake of foods high in polyphenols such as almonds, olive oil, red wine, legumes, fruit, and vegetables. According to Shen et al. (2015) and Martnez-González et al. (2015), following the Mediterranean diet also entails consuming red meat once a month along with moderate amounts of fish, potatoes, and eggs (12, 13). These communities also practise taking rest after meals, common eating customs, extend meal times and engage in standard physical activity (14, 15). The chance of acquiring hypertension, cardiovascular diseases and neurological diseases is decreased by all of these traits when they are combined (16-18).

Polyphenols found in resveratrol and olive oil have antioxidant and anti-inflammatory properties. It is verified that these chemicals are becoming increasingly significant in the control and treatment of recognised neurodegenerative and neuromuscular illnesses (for instance amyotrophic lateral sclerosis, Duchenne muscular dystrophy and spinal muscular atrophy) (11).

Protein enriched Mediterranean diet

Neurological disorder is a significant health issue because of the rising occurrence and acknowledged effects of impairment in older persons. According to observational research, losing weight is linked to a 30%–40% greater chance of developing dementia and occurs at least ten years before either condition is officially diagnosed. Despite the fact that the causes of accidental weight loss in dementia are still poorly understood, there is still time to take action by developing measures to combat undernutrition and postpone or stop the development of dementia (19).

WP1: Project and consortia management

The partnership agreement and data management strategy have been put into place to ensure that the project's outputs and deliverables are delivered while also maintaining scientific excellence and knowledge sharing. Additionally, this WP will create project communications (such as media releases and a project website) and grow the network of representatives from the scientific community, stakeholders, and public and patient involvement (PPI) (19).

WP2: Undernutrition, cognitive decline and dementia risk

There isn't enough data to say whether or not undernutrition affects dementia onset and rate, or whether there are gender differences. To offer better estimates of the impact of undernutrition on cognitive decline and dementia, PROMED-COG will use data from existing cohort studies. It will also uncover factors

that influence undernutrition and weight loss in the general population. Additionally, potential moderating factors on the relationship between undernutrition and cognitive decline will be assessed (19).

WP3: Mediterranean diet, physical activity and neurocognitive ageing

Physical activity (PA) and the Mediterranean diet (MeDi) have both been linked to a lower threat of AD (20-23), but their combined effects may be even more effective(24). To evaluate the possible additive effects of food and physical activity on neurodegeneration and dementia, more study is required because there are only a few studies that provide sufficient data. Biomarkers for neuroimaging using structural MRI, offer sensitive indicators of brain healthiness and may shed light on the potential pathways by which modifiable behaviours contribute to cognitive decline.

The molecular processes that underlie relationships between nutrition and neurocognition have not been extensively studied up to this point. WP3 will address these gaps in science and is headed by the National Research Council, Italy. The hypothesis put forth by WP3 is that a Mediterranean diet improves cognitive function and protects against dementia through positive effects on inflammatory markers, brain structures and body composition mediated by favourable metabolomic profiles and better nutrient intake. WP3 will also investigate the systematic pathways associated with the diet-related neurocognition. To ascertain how the MedDiet might affect circulating metabolites and how the metabolites might mediate the associations between diet and neurocognitive measures, blood samples from the NutBrain cohort will be subjected to metabolomic analysis and inflammatory markers (interleukin 6 and C-reactive protein) (19).

Mediterranean diet in preventing neurodegenerative diseases

The most recent research has looked at the relationships between neurodegenerative illnesses, the MeDi, and the indicators and mechanisms of neurodegeneration. Most of the epidemiological research show a protective relationship between brain health, cognitive impairment, and medical adherence. There is also developing evidence from clinical studies that supports these observational findings. Polyphenols derived from plants may activate related molecular pathways to calorie-restricted diets in terms of their mechanism of action, which aids in explaining the MeDi's neuroprotective effects (25).

Alzheimer's and Parkinson's illnesses mostly impact the ageing population, and neurodegenerative diseases account for a sizeable share of the burden of neurological public health worldwide. The most prevalent neurodegenerative disease, Alzheimer's disease (AD), is predicted to impact 13.8 million people by 2050 (1). Since there are no curative medicines for neurodegenerative disorders now, research focus has switched to finding targets for prevention. Specifically effective people health aims for illness prevention include dietary changes and other modifications to lifestyle and health behaviours.

Researchers hypothesise that well established cardioprotective nutritional patterns, including the Mediterranean diet may be defensive for neurodegenerative illnesses given the link between cardiovascular and brain health (26).

Measurement of Mediterranean diet

The mediterranean diet is characterised by a comparatively more intake of vegetables, legumes, monounsaturated fat, fruits, whole grains, fish, nuts and moderate alcohol drinking, and lesser consumption of red meat, dairy, saturated fat and refined grains. The MeDi shows dietary habits usual among the populations closest to the Mediterranean Sea. There are neither suggested amounts for the MeDi components nor specified cut points. Instead, participants are distinguished within the sample in research studies to recognize those who follow this than the rest of the people in terms of dietary pattern (25).

Memorable food: Fighting age-related neurodegeneration by precision nutrition

Neurodegenerative disorders (NDDs), which mostly, but not only, afflict the ageing population

globally, are posing a severe threat to healthcare systems. PD, AD, amyotrophic lateral sclerosis, and multiple sclerosis are the most well-known neurodegenerative illnesses, but traumatic brain injury and other viral infections of the brain can also result in neurodegenerative diseases. The permanent loss and dysfunction of neurons, which frequently leads to dementia and eventually death, are typical of neurodegenerative diseases.

Genetic variation, epigenetic modifications, the degree of oxidative and nitrosative stress, mitochondrial malfunction, and DNA damage are only a few of the variables that contribute to the pathophysiology of NDD. The intricate interplay of every one of the components may constitute a fingerprint of neurodegeneration, with various diseases being impacted by various aspects to varying degrees.

Numerous studies have been done that demonstrate how regular exercise improves cognitive abilities and brain health. Additionally, a nutritious diet that is balanced in macro- and micronutrients is important for preventing neurodegeneration and halting the progression of disease. Irregularities in lipid metabolism and low-grade inflammation are virtually always present in people with NDD.

The MeDi can improve the lipid and metabolic profiles of people with NDD. The MeDi has been linked in numerous studies to a lower incidence of AD and dementia, although a cause and effect connection is not shown. Caloric restriction experiments demonstrated neuroprotective effects in animal models, however the outcomes in people are erratic. The diseases of NDD are intricate, and (epi)genetic diversity between individuals is significant within any group. Additionally, the gut microbiome is a key component of the gut microbiome-brain axis and is connected to the aetiology of NDD due to its significant involvement in nutrition absorption and lipid metabolism.

Numerous research has been done on the involvement of various micronutrients (such as bioactive polyphenols and omega-3 fatty acids from medicinal plants and fruits) in the prediction, prevention, and treatment of NDD, still individualised dietary advice for NDD patients is still a long way off. Large-scale cohorts are required to do this. These cohorts should include mapping of genetic variants, precise monitoring of food intake, epigenetic data, metabolome, microbiome research, transcriptome and lipidome data (27).

Nutriepigenomics

Nutriepigenomics is the study of how various nutrients interact with DNA. Without changing the DNA sequence, nutrients have an impact on human health via epigenetics in following ways: by encouraging epigenetic modifications and by undoing previously acquired or inherited changes. According to Martin and Fry (2018), toxic xenobiotics can either directly inhibit DNA methyltransferases, causing hypomethylation, or they can remove methyl groups from physiological events where they are present (28). On the other hand, some foods can encourage demethylation and the activation of genes that have been silenced by prior DNA methylation in addition to preventing the hypermethylation of DNA.

To prevent the damage of DNA methylation by air pollutants or another factor, chemicals like B vitamins work as methyl donors (29). Additionally, some bioactive substances have been shown to be able to counteract the epigenome dysregulation brought on by bisphenol A (30), and dietary folic acid supplements have been shown to be effective in preventing the negative effects of heavy metals (31). Vegetables and fruits, as well as the active chemicals they contain, have the capacity to influence DNA methylation through the epigenetics process. Many bioactive substances have been found to have substantial epigenetic potential, including hesperidin, lycopene, lycopene, phloretin, genistein, coumaric acid, caffeic acid, epigallocatechin gallate, and isothiocyanates.

The levels of DNA methylation are affected differently by these substances. Although some of them have hyper methylating action, others have the opposite effect. Resveratrol, which is also present in peanuts, mulberries, and cranberries as well as grapes and red wine, affects histone modification and DNA methylation by inhibiting the activities of histone deacetylase and DNMTs (32).

Microbiota and gut–brain axis

The microbiota of gut impacts the physiological, behavioural, and cognitive functioning of the brain in

addition to nutriepigenetics, however the precise mechanisms are yet unclear. About 1014 different types of microorganisms, including viruses, bacteria, protozoa, and fungus, that make up the intestinal microbiota, which lives in harmony with the host in the gastrointestinal system. According to Wilkins et al. (2019), the disparity in the composition and operation of the gut microbiota, known as dysbiosis, has been linked to the emergence of a number of chronic disorders, including immunological, gastrointestinal, neurological, and metabolic conditions (33). The microbiome may be negatively impacted by a variety of variables, including food additives, diet, pesticides, stress, and antibiotics. The Western diet is characterised mostly by highly processed foods and a high intake of calories.

This diet has a detrimental effect on the composition of the gut microbiota, which influences the brain health and immune system (34). Alternatively, epidemiological data indicate that dietary interventions and calorie restriction by means of specific micronutrients (vitamin B, vitamin C, vitamin D, vitamin E, omega-3 PUFA and flavonoids), macronutrients (fish), prebiotics, and probiotics may delay or prevent age-related neurodegeneration (35).

Biomarkers, and brain atrophy in old age in Alzheimer disease

It has been established how a MeDi affects cerebral abilities and in vivo biomarkers for AD. The German cognitive impairment and dementia cross-sectional analysis data support the idea that MeDi acts as a buffer against memory loss and medial temporal atrophy. They propose that a decline in amyloidosis and tau pathology could account for these relationships. This hypothesis and its consequences for therapy should be further investigated in longitudinal and dietary intervention studies (36).

Studies have demonstrated that the positive relationship between MeDi adherence and memory function, which was observed in this study as well as many others, may be mediated by the maintenance of brain volume in the medial temporal lobe areas. Furthermore, few studies demonstrate an inverse relationship between MeDi adherence and the pathologic indicators for the amyloidosis and tauopathy that underlying AD. Finally, Stern et al findings imply that MeDi helps to maintain brain health since it moderates the correlations between A42/40, pTau181, and brain atrophy (37).

Notably, the exploratory examination of the various MeDi components revealed a favourable correlation between pTau181 and both the A42/40 ratio and the ratio of monounsaturated to saturated fat. Numerous food sources, including plant oils, nuts, seeds, and animal products, include monounsaturated fats, and it is likely that a combination of these sources contributed to the total level in our study. Higher scores for the monounsaturated/saturated fat ratio in Mediterranean regions most likely reflect higher consumption of extra virgin olive, which has been linked to improved cognitive function in PREDIMED trial participants (38) and to reduced AD pathology in mice (39).

Role of nutrition in the modulation of the endocannabinoid system

Worldwide, neurodegenerative illnesses, which are characterised by oxidative stress, neuronal loss, and neuroinflammation are a substantial cause of mortality and morbidity. It is well known that the MeDi has broad-spectrum neuroprotective properties, but it is still unclear if the right mix of nutrients and calories might influence the endocannabinoid system. Endocannabinoid tone augmentation may be a viable new treatment approach to combat the primary symptoms of neurodegeneration, according to numerous studies conducted in recent years. Adaptive balance amongst our ancestors is compromised by the prevailing western diet, leading to a Clinical endocannabinoid deficiency syndrome (40). From a phylogenetic perspective, the co-evolution of human dietary habits and endocannabinoid system could play a significant function in the pro-homeostatic activity of the mediterranean lifestyle.

Effect of bioactive compounds on neurodegenerative diseases

The emergence of neurodegenerative disorders is believed to be significantly influenced by

neuroinflammatory processes in the brain, primarily due to the increased production of reactive oxygen species. Because antioxidant defence systems are less active in the brain than in other organs, the brain is more vulnerable to oxidative stress. Increased oxidative stress contributes significantly to the aetiology of neurodegenerative illnesses like PD, AD, ischemia diseases, and ageing, which is in line with these observations. The MeDi contains bioactive compounds that are linked to the protection of neurological disorders. Through processes like the sequestration of free radicals, the prevention of hydrogen peroxide formation, and the activation of endogenous defence systems, these compounds are capable of exerting significant antioxidant activity (41).

According to Roberts et al. (2012) and Granzotto and Zatta (2014), nearly all neurodegenerative illnesses exhibit similar pathogenic characteristics, for instance the exposure to oxidative stress, formation of misfolded protein deposits and metal ion dysregulation (42, 43). In AD, the intracellular tangles are made of hyperphosphorylated Tau protein, whereas the extracellular senile plaques are composed of amyloid-peptides produced from mutations in the genes encoding the amyloid precursor protein. 70% of elderly dementia cases are caused by AD. According to Plassman et al. (2010), threat factors include diabetes, obesity, hypercholesterolemia, and cardiovascular issues such inflammation and hypertension (44). Modern treatments for neurodegenerative illnesses are ineffective and incurable (45).

Since signs of neurodegenerative illnesses don't manifest in humans until the disease has progressed, finding new treatments and preventing them are two of science's greatest problems. Neurodegenerative diseases are caused by complicated, multiple mechanisms. However, these mechanisms share several pathways, such as oxidative stress, inflammation, intracellular Ca2+ excess, and mitochondrial malfunction. The advantages of therapeutic interventions are frequently limited by the coexistence of numerous paths (41).

Some of the most significant adaptations induced by the Mediterranean dietary pattern includes inflammation and platelet aggregation, protection against oxidative stress, modification of hormones, lipid lowering effect, and gut microbiota-mediated production of metabolites influencing metabolic health and inhibition of nutrient sensing pathways by definite amino acid restriction (45).

Bioactive substances in the Mediterranean diet

Several bioactive components are present in the Mediterranean diet, some of the are listed in Table 1.

Resveratrol

One of the most researched polyphenols, resveratrol belongs to stilbene family and is mostly found in grapes and wine. Takaoka (1940) found this stilbene in Veratrum grandiflorum (47), while Langcake and Pryce (1976) reported finding it in high abundance in Vitis vinifera(48). Numerous advantages of resveratrol have been shown in scientific literature, the majority of which relate to increased cardiovascular health and antioxidant capacity. Resveratrol is a crucial component of the MeDi for neuroprotection, according to pharmacokinetics of the molecule and the

Table 1. Bioactive compounds present in Mediterranean diet (46).

Foods	Sources
Legumes	Phenolic acids, anthocyanins/anthocyanidins, vitamin C
Milk and derivatives	Mineral salts, calcium, water-soluble and hyposoluble vitamins, fats and proteins
Vegetables	Vitamins (vitamin E, vitamin C), minerals (zinc and selenium), antioxidants, phytoestrogens, dietary fiber, flavonoids
Olive Oil	Hydrocarbons, phytosterols, fat-soluble vitamins, polyphenols
Fruits	Sugar, fiber, vitamins and minerals, phenolic content
Meat	Potassium, calcium and iron, vitamin A, B vitamins, vitamin D, vitamin K, chromium, copper, folic acid, magnesium, selenium, n-3 fatty acids
Fish	Mineral salts (calcium, phosphorus, and iodine), vitamin A, B vitamins, vitamin D, proteins
Red Wine	It is a healthy source of antioxidants and its active ingredient, resveratrol. In addition, it is rich in vitamins and minerals.

high quantity of grapes and red wine (41). Presence of resveratrol occurs in a large range of plant bases that are consumed (49).

The scientific community began to identify the health benefits associated with resveratrol, which increased the number of studies mentioning its existence in a variety of plants. Since then, at least 72 foods derived from plants have been found to contain resveratrol (49, 50).

According to Hernandez and Rentero (2018), resveratrol inhibits tauopathy, improves the creation of long-term memories, reduces brain pro-inflammatory responses, prevents the synthesis of amyloid plaque, and delays neuronal death (41).

Melatonin

A typical neurohormone of the pineal gland, melatonin (N-acetyl-5-methoxytyramine) is also generated by plants as a secondary metabolite. It has been established that serotonin, tryptophan, and N-acetylserotonin are eventually used in the production of melatonin. In contrast, melatonin can also be created in yeast by 5-methoxytryptamine being N-acetylated when serotonin is O-methylated (51, 52). In addition to leaves, roots, and fruits from various plants, melatonin has been found in seeds from many plants, including sweet corn and rice. In fact, kiwis, strawberries, pineapples, apples and bananas have all been found to contain melatonin (53).

There are several potential melatonin effects that may be helpful in treating neurological diseases (54). Melatonin has demonstrated the ability to defend the cognitive deficits and suppress the production of nicotinamide. Melatonin can similarly slow the development of amyotrophic lateral sclerosis by preventing loss of MT1 reception (55) and minimise oxidative stress by reducing carbonyls generation (56, 57).

Hydroxytyrosol

According to Mateos et al. (2001), the main forms of hydroxytyrosol identified in olive oil are acetate, secoiridoid derivatives, and free form (58). To extract olive oil from olives, oleuropein, which is hydroxytyrosol esterified with elenolic acid, is present in the olives (53).

The consumption of hydroxytyrosol may also help cure neurodegenerative conditions like AD or PD (59, 60). Hydroxytyrosol can pass the blood-brain barrier just like melatonin. As a result, it can quickly metabolise in the brain and act where the oxidative attack is generated (53).

Numerous research examining the effects of hydroxytyrosol revealed the molecule's significant capacity for neuroprotection. Both in vivo and in vitro, hydroxytyrosol notably reduces LDL efflux in a dose dependent fashion. This information provides a foundation for future research on the possible effects of hydroxytyrosol as a neuroprotective substance (60). Oleuropein's primary degrading component, hydroxytyrosol, is suggested as a prospective chemical for neuroprotection (59).

Polyphenols

A sizable and diverse set of phytochemicals with phenol rings is referred to as polyphenols. They are primarily separated into lignans, stilbenes, phenolic acids, and flavonoids. According to Panday and Rizvi (2009), the five main types of flavonoids are flavonols, flavones, flavanones, anthocyanins and isoflavones. The neuroprotective properties of polyphenols were utilized to stop neurological illnesses (61).

Conclusion

It is challenging for scientists to find strategies to impede the progression of neurodegenerative disorders. Given the link between neuroinflammation in neurodegenerative disorders and oxidative stress, maintaining a nutrition high in bioactive compounds with a known anti-inflammatory and neuroprotective impact may help to slow the progression of the condition and prevent cognitive decline. Neurodegeneration is one of several chronic diseases that the MeDi helps to prevent. This diet is an effective tool for this because it contains a variety of substances with advantageous qualities. When it comes to pathological disorders where oxidative stress and inflammation are critical factors, polyphenols and resveratrol may be a beneficial treatment.

Finding protective variables is difficult since cognitive decline and dementia are etiologically complex outcomes with non-vascular and vascular sources. Since there is little knowledge of impact transformers for the relationship between cognition and MeDi, differences in study populations by race, sex, country of origin, and related threat factors could be involved. To determine when in the life course diet may have the biggest influence on late-life cognition and whether dietary changes made in midlife or late-life have the capacity to reduce neurodegeneration and preserve brain health, continuing longitudinal follow-up studies are required. Additional study is required to determine the protective effects of MeDi on neurodegeneration, the components of MeDi that the population should pay the most attention to, and whether or not these components differ according to race, ethnicity, age, or other variables.

Funding: This work was supported by the National Institute of Biological Resources (NIBR202325101).

Acknowledgements: Declared none.

Conflict of Interest: The authors declare no conflict of interest, financial or otherwise

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Received: 18 July 2023
Accepted: 8 September 2023
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