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Impact of Diet and Intestinal Microbiome on Neurodegenerative Diseases

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ABSTRACT

Diet plays an important role in the health of the individuals such as determining the composition of the gut microbiome. It has been reported that neurodegenerative diseases are associated with changes in diet and the gut microbiome and its metabolites. The balance of bacteria in the intestinal microbiota provides health benefits to the host, and its imbalance plays a role in the development of various diseases, especially neurological diseases, by creating dysbiosis. It also has been observed that beneficial bacteria can prevent or cure the development of neurological diseases by repairing this dysbiosis.

In this review, we discuss how neurological diseases occur, the mechanism of suspicious triggers, the relationship between the intestinal microbiota and neurodegenerative diseases, and whether these diseases can be treated according to diet.

Keywords: Diet; Intestinal; Microbiome; Neurodegenerative; Polyphenols.

INTRODUCTION

Neurodegenerative disease is a chronic disorder that involves a loss of brain neuron activity, causing progressive defacement of cognitive function. Many people suffer from these disorders such as Alzheimer's Disease (AD), Parkinson's Disease (PD), Multiple Sclerosis (MS), and Autism Spectrum Disorder (ASD) [1].

AD is the most common disorder. 50 million people live with AD [2]. This disorder is also progressive and chronic that causes brain cell damage and death. It is also the most common cause of dementia. Some studies have shown that intestinal flora is at a fairly low density in AD patients [3]. AD might be related to daily diet habits. An anti-inflammatory diet pattern may be beneficial because it contains dietary components such as antioxidants and polyphenol [1].

PD is a brain disorder that leads to shaking, stiffness, and difficulty with walking, balance, and coordination. The hallmark of this disease is that the nigra dopamines disappear and accumulation of a-sinuses and a-synuclein occur abnormally and the protein aggregated [3]. In a study conducted on 72 PD patients, it has been observed that patients who have the same age have high amounts of Enterobacteriaceae in their gut. These results may indicate that PD as a neurodegenerative disease may be correlated to the gut [4].

MS is low-grade inflammation, chronic demyelinating, which affects young people, particularly young women. The low-grade inflammation can be affected by pro-inflammatory cytokines, anti-inflammatory cytokines, and intestinal microbiota composition in the body Moreover, the style of the diet can be associated with inflammation in the body such as Western Diet (WD) [5].

ASD is a complex developmental condition that includes persistent difficulties in social interaction and repetitive/restricted behaviors. There is a considerable emphasis on the gene factor in this disease. Clinical trials showed that children with ASD had lower fiber consumption and took less human milk in infancy

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than neurotypical children [6]. Some studies showed that, when compared with pre-treatment, children with ASD who had microbiota transfer therapy had significantly reduced indigestion, abdominal pain, diarrhea, constipation, and significant improvement in behaviors related to autism [7, 8].

Almost all neurodegenerative disorders might be related to the gut flora, its microorganisms, neurological pathways, and daily dietary pattern somehow. Therefore, recent researches have focused on the axis between the brain and the intestine with neurodegenerative diseases which is called the Gut-Brain Axis (GBA), and the gut microbiota [6]. The gut-brain axis is a communication line between the central nervous system (CNS) and the enteric nervous system (ENS). The role of GBA is to monitor the intestine, immune functions, and intestinal permeability [9]. When external stimulation factors affecting people such as environmental stress, it will cause an increase in the systemic pro-inflammatory cytokines, stimulate secretion of the corticotropin-releasing factor (CRF) from the hypothalamus, stimulates adrenocorticotropic hormone (ACHT) and secretion occurs. Consequently, these stimulants lead to a cortisol release from adrenal glands which is a major stress hormone that affects many organs and cells, including the brain such as epithelial cells, immune cells, smooth muscle cells. As a result, when the cortisol hormone increases in the body, inflammation starts and if this condition is permanent, it can cause an autoimmune condition [6].

The colonization of the gut microbiota starts generally at birth when the infant becomes exposed to the maternal microbiota during delivery. Factors determining microbiota content are the mode of delivery, prematurity, breastfeeding, environment, antibiotic exposure, host genetics, stress, maternal infection, and obesity if present [10]. Microbiota mostly contains two main bacteria which are named Firmicutes and Bacteroides. They are located under a group named Phyla. These two main bacteria are very significant for the host homeostasis in the whole life [3, 10].

The relationship between diets and microbiota has been increasingly important nowadays. In this study, mainly the effect of diet on microbiota and the effects of the changes in microbiota on neurodegenerative diseases are studied. The relationship between the brain and the intestine, then the relationship of microbiota with diseases and nutritional contents, and also useful diet types in the fight against neurodegenerative diseases will be discussed.

HOW DO NEURODEGENERATIVE DISEASES OCCUR?

Most neurodegenerative disorders are known to be complex, but most of them have common features such as mitochondrial dysfunction, oxidative stress, which underlies many diseases including, cancer, metabolic disorders, and inflammation [11, 12].

The mitochondrion is an organelle that has a significant role in energy metabolism and other cellular processes such as β-oxidation of fatty acids, regulating the proper concentration of calcium ions in the mitochondrial matrix, amino acid metabolism, and control of cell death. The mitochondrial genome is a small circular DNA molecule and there are many copies of mitochondrial DNA (mtDNA). mtDNA replication is not related to the cell cycle, and any mtDNA mutation can cause the affected cell to proliferate and accumulate [13]. In general, the mitochondria produce ROS during normal metabolism. However, high amounts of ROS production can cause DNA damage, disrupt cell membranes and functions. Consequently, mtDNA mutations and ROS accumulation can contribute to aging [14]. In addition, the changes in energy metabolism might be a consequence of neurodegenerative diseases. Moreover, since cell death is the main feature of neurodegenerative diseases, mitochondrial dysfunction and oxidative damage can lead to neurodegenerative diseases [13].

The intestinal microbiota consists of approximately 100 trillion microorganisms found in the gastrointestinal tract (GIT). The fetal GIT is a sterile environment until delivery and microbiota start to occur after birth. In babies born vaginally, the first colonization begins with Bifidobacteria, Lactobacillus, Bacteroides, Proteobacteria, and Actinobacteria. However, high amounts of Escherichia coli (E. coli), Clostridium, especially C. difficile, and to a lesser extent Bifidobacteria and Bacteroides at cesarean delivery [15]. It is found that infants fed with maternal milk have more Bifidobacteria in the intestine and infants fed with formula have equal amounts of Bifidobacteria, Bacteroides, and Staphylococci in the intestine. Thus, intestinal bacteria could be an important factor for triggering neurodegeneration because some of them can be characterized by some neurodegenerative diseases. For example, children with ASD

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generally have higher amounts of Proteobacteria and Bacteroidetes and lower amounts of Firmicutes and Bifidobacteria compared to healthy controls. Likewise, Prevotella counts are also smaller in autistic subjects, despite the abundance of Bacteroidetes which is important to understand the significance of certain physiological changes in the gut and/or the brain [16].

It is important to assess the populations of particular gut symbionts in addition to quantifying the relative increase or decrease in the populations of certain phyla. It is reported that a low-fat diet with a high amount of plant polysaccharides was switched to a high-fat and high-sugar diet, and this transition changed gut microbiome colonization and metabolic pathways in one day. In general, diets high in animal fat and protein are correlated with Bacteroides, high-fiber diets with Prevotella, and plant-based diets with both Bacteroides and the Firmicutes [17, 18]. Thus, these bacteria may also be associated with neurodegenerative diseases as they are shaped by daily diet habits.

It is reported that inflammatory mediators are activated by microglia and that these infiltrated immune cells trigger intracellular signals. Other causes of neurodegenerative diseases are may be infections, genetic mutations, trauma, and protein accumulation in the CNS with chronic activation of a natural immune response [19]. In addition, environmental triggering and lifestyle are other effective factors that increase the risk of neurodegenerative diseases, for instance, smoking and having a neurogenerative disease in the family. A recent study supports these triggers, for example, showing an increased risk of Amyloid Lateral Sclerosis (ALS) disease which is a neurodegenerative disease that affects motor neurons [20], in humans, as seen in MS in areas with higher concentrations of air pollutants and low vitamin D levels [21].

According to the findings, neurodegenerative diseases may be caused primarily by the dysfunction of mitochondria, which are involved in the energy metabolism of cells, the gut microbiota, some inflammation mediators, infections, genetic factors, and environmental triggers.

Factors Affecting Immune System

Cytokines are a group of small polypeptides. It is quickly upregulated in response to diseases, injuries, and infections. These polypeptides are classified as either pro-inflammatory cytokines or anti-inflammatory cytokines and named depending on their actions in peripheral tissues. Pro-inflammatory cytokine increases the inflammation while anti-inflammatory cytokine decreases it. The chronic microglial pro-inflammatory cytokines are interleukins (IL-1 and IL-6), tumor necrosis factor-a (TNF-a), and interferon-γ (IFN-) has received attention for their role in neurodegenerative diseases because these cytokines are found associated with inflammation and neurodegenerative diseases as well [22].

Microglia cells are special invading immune cells that act as the main inflammatory mediators of the CNS. In a healthy CNS tissue, microglia are small, circular, and dominate a special morphology with numerous branching processes. These cells have critical physiological roles such as removal of neuronal fate, migration, axonal growth, and instant reappraisal during the brain and spinal cord development. This tissue is rapidly activated by many pathological conditions, including altered neuronal function, ischemia, and inflammation. The microglial response to the CNS also causes the initiation of many immune functions such as phagocytosis, antigen processing, and proliferation of both cytotoxic and neurotrophic factors [22-24].

Mediators of cytotoxicity released from activated microglia consist of reactive oxygen and nitrogen species arachidonic acid metabolites, excitotoxic glutamate, quinolinic acid, and histamine [25]. The release of these factors is induced by stimulation of microglia with lipopolysaccharide (LPS), amyloid protein, and a high concentration of IFN-gamma [26]. Microglia-mediated neuroprotection and neurogenesis have been shown to take place due to exposure to IL-4 and low levels of IFN-γ. It may be concluded that microglial actions may be contingent on the nature of the activating stimulus. In addition, some studies have shown that short-term microglial activity is consistently regarded as a neuroprotective role, while chronic activation is concerned as a possible mechanism in neurodegenerative disorders [26].

Evaluating given information, it is thought that cytokines, known as proinflammatory, microglia, and mediators of cytotoxicity can play a role in the development of neurodegenerative disorders by affecting the immune system [27].

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Effects of the Intestinal Microbiome on Neurodegenerative Diseases

As the population ages, neurodegenerative disorders have become more common. Neurodegeneration is a dynamic mechanism that can be caused by environmental stressors such as oxidants, which can cause a gradual degeneration of neurons. Oxidants have been found to cause an imbalance in the metabolism of the gut microbiota by altering the host's endocrine signal [28].

The intestinal microbiota is a dynamic ecosystem and there is a good relationship between the intestinal microbiota and the host. The composition of the intestinal microbiota, where the microbial population is the most concentrated, depends on external factors such as diet. For instance, a high-fat and sugar diet can increase intestinal permeability, lower inflammation, and metabolic status in the gut microbiota [29].

The gut microbiota is not only correlated with digestion, host metabolism, and prevention of pathogenic bacterial colonization but also plays a vital role in the physiological homeostasis of brain functions[30]. Many preclinical and clinical studies have shown that the gut microbiota can significantly interfere with human cognitive functions [28, 30]. In addition, intestinal dysbiosis has been associated with the onset of neurodegenerative diseases such as AD, PD, and MS. Therefore, the gut microbiome can be an important part of the development of neurodegenerative diseases [31].

The gut-brain axis is considered to be a bidirectional neuroendocrine system between the GI tract and the CNS. The relationship between the GI tract and the CNS has been associated not only with intestinal inflammation and eating disorders but also with neurological disorders [32].

There are many overlapping pathways in the communication between the brain and the gut such as the Enteric Nervous System (ENS), the neuroimmune, and the neuroendocrine systems, these systems related to each other, afferent and efferent fibers related to the central nervous system, and the intestine (respectively) [28, 33]. Although the molecular mechanisms are not well understood, there is considerable evidence that suggests that communication is carried out by the afferent neurons of the ENS. These fibers transmit all changes in the GI tract to the CNS and these cytokines released by neuroendocrine cells affect inflammation and infection and neuroendocrine hormones alter intestinal permeability. Thus, by the nervous, endocrine, and immune systems, intestinal microbiota can affect brain functions. Furthermore, the vagus nerve serves as a conduit for the neural connection between the intestinal microbiota and the brain such as microorganisms stimulate afferent neurons of the ENS, and the vagal signal from the gut stimulates the anti-inflammatory response [33].

The microbiota metabolites can have a straight effect on brain functions by act as the production of a neuroactive metabolite. For instance, Short-chain Fatty Acids (SFAs) can trigger the release of neuropeptides from the intestine endocrine cells. In addition, gut microorganisms can be produced by both neurotransmitters and neuropeptides [34]. The short-chain fatty acids, which are the most abundant result of bacterial fermentation, are the signature molecules that mediate microbiota functions. Since SCFA receptors and transporters are expressed in the GI tract, they generally function through traditional endocrine signaling. SCFAs, for instance, regulate serotonin release. Therewithal Peptide YY (PYY), a significant neuropeptide acting at multiple levels of the gut-brain-axis [28, 34].

The biochemical complications of the gut microbiota are less than that in the human brains. Unusually, the hormones which are synthesized by the intestine acts as a neurotransmitter in the CNS. These hormones are serotonin, melatonin, γ-aminobutyric acid (GABA), and acetylcholine. The most crucial inhibitor transmitter GABA which is in the brain is synthesized by Lactobacilli and Bifidobacterium. Noradrenaline, dopamine, and serotonin are also synthesized by Escherichia and Bacillus. The Lactobacilli also converts nitrate to nitric oxide (NO) which is mostly used as a signaling molecule in the nervous system [28, 35, 36]. Thus, they can be important in the treatment or fighting against neurodegenerative diseases.

The majority of neuroactive molecules are involved in the contact between bacteria and bacteria. GABA is made, for example, to protect the organism from the acidic environment found in the stomach. It has been suggested that the role of these small molecules evolved from bacteria-to-bacteria communication to bacteria-to-host communication. Thus, bacteria-bacteria signaling can play a dual role in nervous system regulation, acting on both gut epithelial cells and the ENS [28].

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The communication between the gut-microbiota-brain is not just with neurotransmitters but also, it can be humoral pathways such as tryptophan in the circulation. Tryptophan is a precursor component of serotonin (5-HT). This level is regulated by the intestinal microbiota, and its deterioration is associated with disorders in the brain and GI. The bacterial degradation of tryptophan occurs through kynurenine, the second most common metabolic pathway of tryptophan. Kynurenine is the precursor to kynurenic acid which is a neuroactive molecule. Unusually, a decreased kynurenine/tryptophan ratio is associated with different neurological diseases and genes belonging to the kynurenine pathway, It has been found that it is regulated by the gut microbiota in the hippocampus. The regulation of precursors such as tryptophan and kynurenine can enhance the ability of the gut microbiota to control CNS and ENS neurotransmission [28, 37, 38].

Several studies have been conducted on the metagenomics of the human microbiome. They have shown a strong correlation between the diversity and composition in microbiota and health/disease status. These metagenomic studies have attempted to understand microbial mechanisms. As a result, it has been found that the mechanisms involve microbial interactions that play a vital role in blocking pathogen activities of the infections. In addition, it contributes to health conditions and is closely related to dysbiosis, the onset of neurodegenerative diseases [39-41]. Therefore, new modifications can be applied to that act as a therapeutic agent for the treatment of neurodegenerative diseases such as probiotics and prebiotics.

Probiotics are recognized as living organisms that benefit the health of the host. For instance, Lactobacillus and Bifidobacterium are the best-known probiotics. They have been associated with host immunomodulation [42]. For example, in a study, Bifidobacterium infinities were found to normalize the IL-10/IL-12 ratio [28]. These interleukins are predominantly pathogen-activated antigen-forming cells. Therefore IL-10 and IL-12 are significant immunoregulators in host defense and immune homeostasis [43]. Prebiotics are recognized as food that activates the growth of beneficial microorganisms influences the composition of the intestinal microbiota. The best prebiotics includes the Inulin-type Fructans (ITF), Fructo-oligosaccharides (FOS), and Galactooligosaccharides (GOS). The prebiotics that supports the growth of certain bacterial species can cause major changes in the composition of the gut microbiota [44]. Thus, using prebiotics could be a further strategy for regulating the microbiota-gut-brain axis and then can treat neurodegenerative diseases [45]. For example, some studies have shown that prebiotics shows promising results in both humans and animals. According to these studies, an increase of the N-methyl-d-aspartate Receptor (NMDAR) signal which is required for neuronal growth and survival has been observed [46-48]. So, increasing NMDAR could be beneficial for neurons.

EFFECTS OF DIETARY POLYPHENOLS ON THE INTESTİNAL MICROBIOTA

Dietary polyphenols are a class of secondary metabolites which mostly found in fruits, vegetables, wine, tea, extra virgin olive oil, chocolate, and cocoa. They are predominantly flavones, isoflavones, flavonols, catechins, and phenolic acids derivates. Polyphenols in food have various biologically significant activities, including protection defense oxidative stress, and degenerative illnesses. The majority of these biological activities, according to experimental evidence, can be due to their antioxidant capacities [49, 50].

Neurodegeneration could be related to oxidative stress and it is suspicious pathogenesis of neurodegenerative diseases [28]. It also causes biological macromolecules such as lipids, proteins, and nucleic acids to undergo oxidative changes and it is thought to be very important in the etiology of aging and degenerative disorders. Therefore, dietary polyphenols have been investigated due to their high antioxidant capacity and their ability to regulate cell functions [50]. According to a study, they have been found to play a strong protective role against neurodegeneration and neurotoxicity, and their bioactive components provide a positive effect against neurodegenerative diseases [12]. New treatment strategies, using antioxidants for protection or decreasing the oxidative stress on the regulatory genes can be effective both in aging and neurodegeneration. These implementations aim at increasing neural response by naturally via dietary foods that contain neuroprotective agents like polyphenols [28]. Simply put, polyphenols alter cell pathways and cause cell death through apoptosis and autophagy. This creates a response to nutrient deprivation. In neurodegenerative diseases, triggering autophagy is a very important treatment and prevention [12]. Therefore, consuming foods with high polyphenol content can be beneficial for neurodegenerative diseases.

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Non-absorbed polyphenols and their metabolites that can reach the colon may affect the intestinal flora and regulate the intestinal composition via different mechanisms [51]. It has been reported that polyphenols can regulate the ecology of the intestinal microbiota using anti-microbial activity or prebiotic-like effects against harmful gut bacteria [52, 53]. It is reported also that decreasing the Firmicutes/Bacteroidetes ratio and inducing the colonization of certain beneficial bacterial species can afford protection across some health pathologies [54]. A study on pomegranate found that ellagitannin high in polyphenol significantly reduced the growth of Clostridium bacteria and S. aureus [55]. Additionally, another study found that pomegranate ellagitannin may increase the amount of Bifidobacteria spp. and Lactobacillus-Enterococcus [56].

Many studies have been investigated the effect of dietary sources rich in polyphenols on the intestinal microbiota. For instance, bioactive components of green and black tea, which are hydrolyzable tannins, can suppress the growth of many pathogens such as Helicobacter pylori, Staphylococcus aureus, E.coli. Also, green tea polyphenols can reduce Firmicutes/Bacteroidetes and increase Prevotella/Bacteroides rates [57-59]. Moreover, drinking cocoa can increase Lactobacillus, Bifidobacterium, and Enterococcus bacteria in human intestinal microbiota [60]. In conclusion, several studies have shown that dietary polyphenols can regulate cellular functions with active neuroprotection [28].

BENEFICIAL COMPONENTS OF TEA AND DIETARY APPROACHES

Tea is the most consumed beverage in the world and most of the regions have a cultural type of tea. Green, black, and oolong tea is the most consumed and made from the same plant that is Camellia Sinensis. Many studies have investigated the protective effect of teas on many diseases, including neurogenerative diseases. Green tea is the most investigated one. It contains several chemical components and these components can affect brain functions [61]. These components include green tea catechins (GTCs), caffeine, and theanine. However, the main component is epigallocatechin-3-gallate (EGCG) because it acts as an antioxidant by neutralizing free oxygen species and it has anti-inflammatory effects as well [62]. For more than 20 years, cell and animal experiments have been studied the relation between gene/protein expressions and green tea catechins (GTCs). The results showed that green tea and GTCs act on inflammation-related genes such as TNF-a, IL-1B [62]. A comprehensive review article shows that these bioactive ingredients can be used against neuron degeneration in the future. In another pooled analysis of a total of 26 observational studies, associations between tea consumption and cognitive dysfunctions reduce the risk of cognitive impairment. On the other hand, some epidemiological studies have shown that tea has a clear protective effect on PD patients. In another controlled study, 249 PD patients and 368 controlled groups were compared and found that black tea, coffee, Japanese and Chinese teas had an inversely proportional relationship to PD. Finally, some human studies have found that consuming green tea has a beneficial effect on cognitive dysfunction and memory loss [61]. These mentioned studies support the beneficial effects of tea consumption, yet further studies are required to estimate the relation between tea consumption and neurodegenerative disorders.

Beneficial Components: Flavonoids and Curcumin

The flavonoid plant metabolites have been studied intensively in the treatment of neurodegenerative disorders due to their high antioxidant capacity. As mentioned earlier, flavonoids are found in large amounts in beverages such as fruits, vegetables, red vine, and tea. Also, it is rich in flavonols such as green tea, cocoa, catechin, and epicatechin. The citrus fruits are also rich in flavanones such as naringenin and hesperetin and the fruits are rich in anthocyanins such as cyanidin and malvidin. These biochemical components are beneficial and can be investigated by more future studies about neurodegenerative disorders [63].

The antioxidant capacity mechanism of flavonoids is not clear because flavonoids are exposed to too much metabolism in the gastrointestinal system and, as a result, antioxidant capacity decreases. However, according to recent studies, a protective effect was observed in *in vitro* studies against age-related cognitive and motor dysfunctions. These neuroprotective effects may have suppressed the activation of microglia, which alleviates the inflammatory process in the CNS. Other example evidence from animal and *in vitro* studies has supported the idea that flavonoids can cross the BBB and remain in the brain. Therefore, flavonoids have been considered as a potential anti-neuroinflammatory factor. Neurodegenerative disease is

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a complex pathological condition and the use of dietary components such as flavonoids that show the most functional activity in the brain could provide a good preventive treatment against neurodegeneration [63].

Curcumin is one of the powerful antioxidants. It is a natural polyphenolic, yellowish component. In addition, it has been used in the treatment of neurological disorders for centuries due to its antioxidant and anti-inflammatory properties. It not only traps free radicals due to its antioxidant capacity but also improves memory. Studies have shown that curcumin has a neuroprotective effect and is effective against Alzheimer's, depression, and seizures. It also protects lipopolysaccharide (LPS) toxicity by inhibiting nitric oxide (NO), prostaglandin E2 (PGE2), ROS, and proinflammatory cytokine production. LPS is a bacterial endotoxin and is used in animal studies to assess inflammation that triggers neuroinflammation and between brain function and memory impairments. Most studies have found that LPS and other toxic agents such as ethanol and d-galactose activate ROS-induced neuroinflammation. The effectiveness of the curcumin is because of being a potential antioxidant, anti-inflammatory, and against LPS-induced ROS-mediated neuroinflammation, neurodegeneration but still needs much evidence about that [64]. Looking at current studies, there is no cure for the progression of neurodegenerative disorders, but lifestyle modification, exercise, and taking natural polyphenol capsules can be beneficial in preventing the onset of these neurodegenerative diseases [64].

Dietary Approaches

Systemic inflammation is common in most chronic diseases' etiology including neurodegenerative disorders. This inflammation can measure different markers such as interleukins (ILs), tumor necrosis factor-a (TNF-a), and highly sensitive C-reactive protein (CRP). IL-17 and IL-17A are also pro-inflammatory markers especially IL-17A which is very high in chronic disorders associated with autoimmunity such as MS. Many researchers have attempted to find a relationship between dietary patterns and inflammatory markers. For instance, a cross-sectional study found that the relationship between a healthy diet and inflammation was inverse. However, the Western diet was found to increase inflammatory markers [65]. In the following section, we will address how dietary patterns especially MED, DASH, and KD affect human health and neurodegenerative disorders.

The Mediterranean Diet (MED)

The Mediterranean diet (MED) is one of the most beneficial diets proven so far. According to the epidemiological studies and controlled clinical trials, the MED reduces the whole mortality, the risk of cancer, protects from cardiovascular disease, and improved type 2 diabetes mellitus outcomes. That's why it might be thought that it protects or treats neurodegenerative diseases. The MED consists of long-chain omega-3 fatty acids such as fresh fish, canola oil, almonds, and walnuts. It is a rich source of polyphenols especially flavonoids sources such as grains, vegetables, fruits, olive oil, red vine, tea, chocolate, and coffee. It also consists of probiotics just as yogurt and fermented products. The nutrients, other bioactive components such as fiber, folic acid, phytosterol, and antioxidants, all of them are playing an essential role in protective effects against diseases [66].

The main ingredient of the MED is olive oil and its beneficial properties come from essential fatty acids. The essential fatty acids are not synthesized in mammals and must be taken from a daily diet. These essential fatty acids are linoleic acid (LA), a-linoleic acid (ALA), and arachidonic acid (ARA). ALA is required for the synthesis of the long omega-3 fatty acids along with eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) [66].

The ALA is converted to EPA in humans but DHA synthesis is less. Also, omega-3 fatty acids are easily oxidized, and the effects of antioxidant foods such as those containing polyphenols may also be helpful. But not all omega-3 fatty acids are beneficial because according to a study, chia seeds have been shown that it has harmful effects in animal studies with AD [67]. Consequently, it is necessary to consume fish, seafood, or take a fish oil supplement for EPA and DHA fatty acids to get these health benefits.

DHA is mainly found in the brain and retina in humans. It crosses to the fetus by the placenta and regulates the neuronal signaling pathways by glial cells. Also, DHA is important for learning and improve memory. A study has shown that preterms who consumed maternal milk had higher IQ and better short-term memory and attention than preterm who consumed formula [68]. With aging, the DHA concentrations

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reduce in the brain with AD patients. This reduction is possibly caused by the much consumed omega-6 fatty acids in the whole lifetime. According to another study, it has been found that a diet rich in DHA has reduced 70% of the total AB load with the AD model in the brain of the transgenic mice [69].

LA is an essential fatty acid, omega-6, obtained from olive oil, corn oil, sunflower oil, and peanut butter oil. There are two enzymes to make long-chain fatty acids, D-desaturases, and elongations, as well as desaturations of omega-3 and omega-6 fatty acids. A diet rich in LA and other omega-6 fatty acids inhibits omega-3 fatty acids and leads to EPA deficiencies. Conversely, increasing α-linolenic acids inhibit omega-6 metabolism. This result also explains why the Eskimo population consumes high amounts of fish oil, but the serum linoleic acid levels are low [66].

In the clinical trials, DHA + EPA supplementation has shown efficacy against mild cognitive impairment (MCI) but not in AD patients. These omega-3 fatty acids are thought to be able to protect age-related cognitive functions of polyunsaturated fatty acids (PUFAs). Most prospective cohort studies have been found that consuming fish is a protective factor for AD. In the other cohort study, a high omega-3 fatty acid diet was followed for 4 years and the risk of cognitive function was low. On the contrary, high consumption of stearic acid and omega-6 doubles the risk of cognitive functions[66]. In conclusion, omega-3 fatty acids can be beneficial effects, especially in AD patients due to their antioxidant, anti-inflammatory, anti-apoptotic and neurotrophic properties.

The Daily Approaches to Stop Hypertension (DASH)

The Dietary Approaches to Stop Hypertension diet contains a high amount of fruits and vegetables similar to the MED. It also consists of low-fat dairy products; dietary fibers, potassium, calcium, and magnesium; slightly high in protein; and a low amount of saturated fat, cholesterol, and total fat. This dietary pattern was developed to treat hypertension [65]. It has been reported that the DASH dietary pattern may be beneficial to health in cognitive functions related to AD patients. In a randomized trial, the DASH diet showed progress in neurocognitive and psychomotor functions in older adults [70]. In addition to the DASH model, there is also another suggested dietary pattern, the Mediterranean-DASH diet intervention for Neurodegeneration Delay (MIND diet), which has been recently defined [70].

The MIND diet is a regulated version of the MED diet, but also it contains additional foods depending on the evidence. It consists of a high amount of plant foods, mostly green vegetables, fruits, less meat consumption, moderate intake of alcohol, and olive oil as a primary fat source. It is reported that berries may protect against neurodegeneration [71]. This dietary pattern is rich in antioxidants and monounsaturated and omega-3 fatty acids which is also beneficial for health and low in saturated fat. These nutrients are individually associated with cognitive performance as mentioned earlier. In addition, there is an association between higher consumption of monounsaturated fat and omega-3 fatty acids and lower risk of cognitive decline and dementia, although higher saturated fat consumption is shown to increase the risk of cognitive decline and dementia. According to this study, the MIND diet is significantly related to better cognitive function and performance [71].

The Ketogenic Diet (KD)

The Ketogenic Diet (KD) has been used normally for three decades for the treatment of epilepsy patients. In addition to epilepsy treatment, it has been reported that the KD pattern can be beneficial against most diseases such as obesity, polycystic ovary syndrome, cancer, and diabetes [72].

Glucose is very important to the brain tissues because it is the main source of energy for them. It has been reported that the ability of the brain to use glucose pathologically decreased, and especially the brain glucose metabolism decreased by 20-40% in AD [73]. When the hunger for a long time or when there is no carbohydrates consumption, free fatty acids are produced for energy use, but the CNS cannot use these fatty acids as an energy source because free fatty acids cannot exceed the blood-brain barrier (BBB). After 3-4 days without carbohydrates consumption, the CNS gets its energy from ketone bodies. These ketone bodies are acetoacetate, 3-hydroxybutyrate, and acetone [72].

The KD generates a metabolic shift from glycolytic energy production against oxidative phosphorylation energetic by using free fatty acids as a first energy source in the human body. As these free fatty acids endure beta-oxidation and ketones are produced. Increasing the oxidative phosphorylation with ketone

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bodies modifies the tri-carboxylic acid cycle to limit ROS production. In addition to that, the ketone bodies transported across the BBB adjust antioxidant pathway genes and also boost energy production in the brain tissue [74]. Thus, it was thought that KD could be beneficial against neurodegenerative disorders.

In humans, the ketones delay infusion, reduce the hormonal response to acute hypoglycemia, and promote cognitive function B-hydroxybutyrate (B-OHB), a type of ketone body, comes to protect neurons from beta-amyloid toxicity characterized by AD [72]. According to a study, it has been revealed that acute elevation of serum B-OHB levels with an oral dose of medium-chain triglycerides (MCT) can improve memory and attention in patients with AD or mild cognitive impairment. According to an *in vitro* study, the addition of B-OHB has been shown to protect hippocampal neurons from AD toxicity, which supports the previous study. It is suggested that it may play a potential therapeutic role for KD on AD-associated mitochondrial deficiency. Also according to an animal study, long-term feeding of middle-aged mice with ketone esters, approximately 8 months, improved cognition, AB, and tau pathology which is characterized with AD [73].

It is also suggested that changing the diet style may be beneficial to the motor and non-motor symptoms in PD. According to a study on the effects of the KD on PD, which compared a low-fat diet versus a ketogenic diet, they randomized 47 patients, which are 44 commenced the diets and 38 patients completed the study. The KD group is generally physiological ketosis. In the low-fat group, the disease symptoms have decreased such as urinary problems, pain and other sensations, fatigue, daytime sleepiness, and cognitive impairment. Both groups have been significantly decreased their disease scores. In conclusion, either the low-fat diet neither the ketogenic diet enhanced motor and non-motor symptoms. Withal, the ketogenic group has been shown more development in non-motor symptoms [75].

Some preclinical studies have assessed the benefits of the KD in the experimental autoimmune encephalitis (EAE) mouse model of MS disease. EAE mouse has been fed with KD and it has shown positive effects such as reversed motor disability, improved learning and memory, increased hippocampal volumes, and re-myelination of lesions. These benefits indicate that KD is related to suppressed production of inflammatory cytokines and changed neuronal repair [76].

In some studies on ASD, it has been found that KD can be helpful against the symptoms of the disease. ASD, as it is known, is a neurodevelopmental disorder and both gastrointestinal dysfunction and intestinal microbiota diversity disorder have been observed in this disease. In a study, mice were fed a standard formula or KD for 10-14 days and stool samples were collected during the diets. Based on these samples, it was shown that the consumption of KD can cause an anti-microbial-like reaction by reducing the total amount of host bacteria in stool samples. In addition, the low Firmicutes/Bacteroidetes ratio of KD counteracts the normal ASD phenotype. It has been concluded that KD consumption may affect the gut composition and some neurological symptoms associated with ASD may be alleviated [76].

CONCLUSION

The composition and diversity of the individual's intestinal microbiome are determined by several factors and the most important of all, is his diet. The intestinal microbiome has been found effective in neurodegenerative diseases. It can trigger these diseases, but also, it can treat these diseases. According to current understanding, there might be beneficial approaches such as a healthy diet pattern and taking in some important bacteria for the host like probiotics and prebiotics.

MED, DASH, and KD dietary approaches have mostly been studied in terms of their relations with neurodegenerative diseases. These diet models can be beneficial in these diseases as they support general health. Probiotics and prebiotics are useful for neurodegenerative diseases because they can regulate intestinal dysbiosis and host homeostasis depend on the bacteria types.

In summary, dietary approaches do not cure neurodegenerative diseases but may help slow the disease outcomes and control them better. Intestinal microbiota and dietary approaches may be one of the treatment goals in the fight against neurological diseases.

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