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Alternative Treatment Options for Alzheimer's Disease: How Antioxidants, Vitamins, Diet and Exercise Can Change Disease Outcome

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Abstract

Alzheimer's disease is a progressive neurological illness with a complex etiology that is the largest cause of dementia in the globe. The mechanism of Alzheimer's disease is complex, but it is defined by the formation of ß amyloid plaques and neurofibrillary tangles. Current allopathic treatments are focused on increasing the neurotransmitter Acetylcholine in synaptic clefts, but they are largely ineffective at improving disease prognosis. Holistic alternatives are suggested to further improve symptoms in patients with mild disease or as a prophylactic to slow the onset for those with a higher predisposition for the development of AD. Exercise improves blood flow to the brain and thus is correlated with improved cognitive functioning and tissue mass. Diets high in saturated fats show poor prognosis as they are correlated with a higher incidence of neuroinflammation, thus diets higher in unsaturated fatty acids such as the Mediterranian diet are recommended. The accumulation of ROS can lead to mitochondrial dysfunction and eventually neuronal degeneration. Of the antioxidants, curcumin has shown to be an effective protective agent against inflammation and oxidative damage. Transgenic AD mice administered curcumin had a significant reduction in oxidative proteins in four different brain regions when compared to control groups. Interleukin-1β, an inflammatory marker, was also significantly reduced with the addition of curcumin. The administration of essential vitamins plays a key role in neuroprotection. Deficits in both vitamin A and D have shown to have a significant reduction in cognition in both laboratory animals and humans. Administration of vitamin A in transgenic AD mice showed a marked reduction in Aβ phosphorylation by decreasing CDK5 kinase activity. In laboratory settings, vitamin D3 has been demonstrated to induce Pgp mRNA to pump Aβ plaque out of cortical circulation by expression of MDR1 genes. While all holistic treatment options show slight improvements in patients with mild disease, they do not prevent disease progression. Further, holistic treatments do not show improvements in patients with advanced disease. Overall, the prognosis for AD remains grim.

Keywords: Holistic treatments • Cholinesterase • Anti-inflammatory

Introduction

Alzheimer's Disease (AD) is a multifaceted neurological disorder. Currently, 47 million people worldwide suffer from dementia [1], with Alzheimer's disease accounting for 70% of this figure [2]. As a result, it is the leading cause of dementia. Alzheimer's disease can be hereditary or sporadic, and it can appear late or early in life [3]. A mutation in the Amyloid Precursor Protein (APP) gene or the Presenilin genes, PSEN1 and PSEN2, could cause familial Alzheimer's disease (involved in APP processing). Sporadic Alzheimer's disease is more common and often found in the elderly above the age of 65; consequently, it is also known as late-onset Alzheimer's disease [3]. As a result, age is the most essential risk factor. Cases diagnosed before the age of 65 are referred to as early-onset dementia, and they are generally related with a family history of dementia. The extracellular accumulation of insoluble ß Amyloid (A) plaques and the intracellular aggregation of neurofibrillary tangles (composed of hyperphosphorylated tau protein) in the cortical and limbic parts of the brain have been related to AD development [1]. Insoluble A fibrils infiltrate into synaptic clefts and disrupt signalling. As a result, plaques form kinases that hyperphosphorylate the Tau protein, causing it to polymerize into insoluble neurofibrillary tangles. These then congregate in the cytoplasm of neurons.

Unfortunately, the current allopathic treatment options for AD are minimal and are only effective for symptomatic relief [4]. Cholinesterase inhibitors such as donepezil, rivastigmine, and galantamine are the first-line therapies for early-onset AD [5]. These drugs function by increasing the neurotransmitter Acetylcholine in the synaptic clefts [5]. In more advanced AD patients, memantine is used for symptomatic relief. This drug can act as both a dopamine agonist and a non-competitive N-methyl-D-aspartate receptor antagonist [6].

Non-Steroidal Anti-Inflammatory (NSAIDs) are used to alleviate systemic inflammation and pain. There is evidence that common over-the-counter non-steroidal anti-inflammatory drugs such as ibuprofen and aspirin can also treat symptoms of early AD [7]. Furthermore, the NSAID diclofenac has also been implicated as a potential treatment for AD [8]. Diclofenac's chemical structure is similar to the fenamate NSAID class [9], which is neuroprotective towards AD [10]. Further studies using US veterans showed that diclofenac could decrease the risk for AD development and slow cognitive decline [8,9].

The lack of a known cure and slight improvement in patients with AD treated with standard allopathic methods has led to the push to explore alternative holistic options [11]. Although there is no cure for AD, holistic treatments can slow progression, manage symptoms, and be used as a neuroprotective prophylactic.

One such holistic intervention is incorporating exercise into the routine of an AD patient early into the disease progression. Morris et al. found that when mild to moderate patients embarked on an exercise regimen, they were shown to have greater blood flow to the brain. These patients had greater hippocampal mass and improved cognitive performance compared to those with the disease who did not exercise [12]. These patients started

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at 60 minutes per week and safely titrated the duration of activity until they reached the public health guideline's recommended time of 150 minutes per week for 26 weeks. The types of exercises tested were both aerobic and toning and stretching, with aerobic exercise showing better outcomes [12].

In addition to increased blood flow to the brain, which improves memory performance and slows the cognitive impairment seen in patients with mild to moderate AD [11], exercise is also helpful in managing weight. This can be harnessed as a prophylactic tool to prevent or slow the onset of AD. The western diet is high in saturated fats and highly implicated in the prevalence of obesity. Not only is this linked to cardiovascular disease, but it also disrupts the homeostasis of the brain and leads to neuroinflammation [13]. Further, studies show that obesity secondary to the western diet leads to cerebrovascular dysfunction in the form of a compromised Blood-Brain Barrier (BBB). This, in turn, induces an accumulation of myeloid cells in the brain's white matter leading to white matter damage and myelin loss [13].

The connection between the gut and the brain is an emerging discovery gaining traction in research. This stems from the idea that disruptions of the gut secondary to dysbiosis lead to an inflammatory response from the body, extending to the brain and leading to neuroinflammation [14]. This neuroinflammation can be due to altered microglial activation and reactive astrocyte activation due to chronic systemic inflammation, leading to an accumulation of Aβ [14]. For this reason, it is recommended that the western diet is avoided and swapped for a diet with less saturated fat [13]. Incorporating aerobic exercise into a daily routine is also suggested to mitigate the effects of poor diet [15]. Additionally, studies indicate that the consumption of antioxidants like green tea (Camellia sinensis) is neuroprotective by decreasing inflammation and regulating the accumulation of Aβ implicated in AD pathogenesis [16].

While there is no single gene implicated in the pathogenesis of AD, a polymorphism of the gene for Apolipoprotein E (APOE) is linked to the onset of Alzheimer's [17]. The gene for APOE can be found in the population in multiple isoforms notably, APOE ε2, APOE ε3, and APOE ε4 [18]. It has been observed the carrier status of APOE ε4 is associated with an increased risk for the development of AD, with APOE ε3 being the most common isoform in the population and APOE ε2 is associated with a decreased risk for the development of AD [17]. Bernath found that those who were carriers for APOE ε4 showed a reduction in polyunsaturated triglycerides. Decreased polyunsaturated triglycerides were also linked to decreased cortical thickness [18]. This brings about interesting research which shows that increasing the intake of polyunsaturated fatty acids like Omega-3 in the form of a single seafood meal per week shows a decreased prevalence of the degenerative neuropathology of AD in those that are APOE ε4 positive [19].

The accumulation of inflammation and oxidative damage has been proposed as an explanation for the neuronal degeneration found in Alzheimer's disease. As a consequence of aerobic metabolism, Reactive Oxygen Species (ROS) develop sporadically in mitochondria [20]. The continuous production of ROS leads mitochondrial malfunction and aggregation [21]. Curcumin, a molecule found in turmeric, is a powerful natural source of antioxidants (Curcuma longa). Curcumin has been used for ages in India, China, and Southeast Asia as a flavouring, textile colour, and traditional medicine [22]. Turmeric has been utilised in traditional Ayurvedic medicine in India to treat a variety of common ailments.

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Curcumin has anti-apoptotic, antioxidant, and anti-inflammatory properties that protect tissues from the harmful effects of ROS [25]. The antioxidant properties are due to curcumins phenol moiety and its ability to donate protons to ROS [23]. In animal studies, APPSw transgenic mice that contain a human familial AD amyloid precursor gene were treated with a low dose of curcumin. When comparing the presence of interleukin-1β, an indicative marker for AD, the group treated with curcumin had a significant decrease of 61.8% in the amount of interleukin-1β when compared to the control group [26]. Curcumin possesses anti-apoptotic, antioxidant, and anti-inflammatory characteristics that protect tissues from the damaging effects of Reactive Oxygen Species (ROS) [25]. Curcumin's antioxidant capabilities are attributed to its phenol moiety and capacity to donate protons to ROS [23]. Curcumin was given to APPSw transgenic mice, which possess a human familial AD amyloid precursor gene, in animal research. When evaluating the presence of interleukin-1, a suggestive marker for Alzheimer's disease, the group treated with curcumin had a substantial drop of 61.8 percent when compared to the control group [26].

The incorporation of fat-soluble vitamins has shown promise for the treatment of AD. The fat-soluble retinoids, a collective group that makes up vitamin A, are essential in a range of neuronal activities, including neurotransmitter release and strengthening of long-term potentiation [27]. Retinoids are commonly found in two forms; preformed retinol from animal products and provitamin A carotenoids found in plant sources [28]. During embryological development, the active compound of vitamin A, Retinoic Acid (RA), coordinates the growth and differentiation of segments in the CNS. In adults, retinoic acid has been shown to promote neural plasticity, a critical aspect in forming new memories and cognition [29]. Animal studies suggest that treatment with All-Trans Retinoic Acid (ATRA) can prevent Aβ plaque accumulation. Transgenic mice, which contain β-Amyloid Precursor Protein (APP) genes, were used as AD model organisms. The test group that was administered ATRA had a 70% and 60% decrease in the frontal cortex and hippocampus accumulation of β-amyloid precursor protein phosphorylation, respectively, compared to the control group [30].

Vitamin D is a fat-soluble vitamin that can either be consumed in the diet either as D3 (cholecalciferol) or D2 (ergocalciferol). Vitamin D3 is synthesized in the skin from 7-dehydrocholesterol on exposure to ultraviolet radiation. The biologically active form, vitamin D3, has been shown to have neuroprotective effects, including antioxidant and anti-inflammatory properties and improved cognitive function in patients with mild AD [31]. Inversely, low serum vitamin D3 concentrations have been measured in patients with AD and associated with decreased cognitive performance [27]. One possible explanation for improved cognition with vitamin D3 supplementation is its interaction with p-glycoproteins (Pgp). Pgp expressed via the Multi-Drug Resistant 1 (MDR1) protein gene assists in the clearance of Aβ plaque accumulation through the BBB, with low Pgp densities observed in AD patients [32]. Animal models have shown that vitamin D3 binds to Vitamin D Receptors (VDR) on the MDR1 gene, inducing Pgp mRNA expression by up to 70% [33]. The results for the animal study showed an increased clearance of Aβ plaques by up to 30% and an overall improvement of cognition in AD transgenic mice compared to the control.

There is a substantial population of individuals living with dementia, and AD presents as a significant contributor. Because of the poor health outcomes associated with AD diagnosis, we aim to explore alternative treatment methods in conjunction with current allopathic treatments to manage AD symptoms to slow progression and reduce morbidity.

Literature Review

Current allopathic treatments

Cholinesterase inhibitors: Cholinesterase inhibitors such as donepezil, rivastigmine, and galantine are considered the first-line therapies for AD symptomatic relief [4]. Acetyl cholinesterase is the enzyme found in the synaptic clefts of neurons responsible for the metabolism of the neurotransmitter acetylcholine [5]. Much of the pathophysiology of AD is

related to the loss of Acetylcholine production [5]. Therefore, inhibiting this essential neurotransmitter's degradation is necessary for the treatment of AD. Inhibition of acetyl cholinesterase increases acetylcholine in synaptic clefts, leading to greater activation of cholinergic neurons throughout the CNS [5].

Memantine: As AD progresses and symptoms worsen, meantime can be added to the pharmacologic regimen to increase symptomatic relief [6]. The drug is a noncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist (Weller 2018). NMDA receptors are inotropic glutamate receptors that are abundant through the CNS (Morrotta). Inhibition of these receptors leads to acetyl cholinesterase inhibition, reduction in protein aggregation, and antioxidant effects [6]. Its efficacy and safety were tested in a 24-week double-blind study of 677 men and women being treated with cholinesterase inhibitors for AD [34]. Participants who received memantine performed significantly better in cognitive and behavior testing than placebo [34].

NSAIDs: Non-Steroidal Anti-Inflammatory Drugs (NSAID) are common over-the-counter pain relief drugs that inhibit cyclooxygenase (COX) [7]. COX is an essential enzyme for the production of inflammatory prostaglandins, and its inhibition subsequently decreases inflammation. This mechanism has proven to be beneficial in treating the early cognitive symptoms of AD [7].

Diclofenac: Diclofenac is an NSAID with a chemical structure similar to the fenamate NSAID class (Daniels 2016). Fenamates are known to inhibit the NLRP3 inflammasome, which is hyperactive in AD [10]. Diclofenac is also known to be transported into the CNS, where it has a significant impact on decreasing amyloid buildup and thus slowing cognitive decline (Rivers 2020). In a retrospective study on US Veterans taking NSAIDs, patients who were taking diclofenac for >1 year showed a significantly lower incidence (.28%) of AD compared to groups taking naproxen (1.66%) and etodolac (2.24%) (Stuve 2020). Therefore, diclofenac shows tremendous promise as a treatment for Alzheimer's disease.

Holistic approach to treatment

Being the most common neurodegenerative disease in the elderly population, it's no surprise that Alzheimer's is the subject of multiple studies that look at medical interventions to reduce the associated symptoms. Unfortunately, given the lack of breakthroughs in finding a curative treatment in allopathic medicine, many researchers have switched to holistic remedies to alleviate symptoms and improve quality of life.

Exercise

A significant issue for individuals who suffer from AD is the lack of independence with disease progression. This not only leads to the need for a caretaker in mild to moderate disease states but ultimately the transfer to a care facility with severe disease [35]. The inability to perform the tasks of daily life is implicated in the morbidity of the disease [15]. However, it has been shown that performing physical activity every day helps to maintain independence for a more extended period [15].

Sobol found that patients who had mild disease and exercised in the form of moderate to high intensity aerobic cardiorespiratory exercises such as stationary bike or treadmill showed increased VO2 peak, which is an indicator of increased cerebral blood flow and thus increased oxygen intake. The study was a 16-week course with three sessions per week lasting about 40 minutes. Results showed that aerobic exercise was associated with cognitive improvements such as improved memory and positive effects on neuropsychiatric symptoms like improved mood [15]. Studies have found that aerobic exercise can significantly influence brain architecture. Cui et al. found a positive association between activity and hippocampal volume and thus better spatial memory and decreased decline in the myelination of the fibers in the corpus callosum [11].

Obesity and diet

Many components in AD development are intrinsic to a person, for example, their genetic makeup. Among those, there are modifiable risk factors known to have contributory risks that increase AD susceptibility [36]. This is because factors such as diet and obesity contribute to neuroinflammation, which has been implicated as the root of cognitive dysfunction in the aging brain [36].

The main contributor to the high incidence of obesity and increased weight in the population is the ingestion of a high-fat diet [36]. The constant state of over nutrition resulting from overconsumption of a high-fat diet brings about inflammatory changes including oxidative stress and increased pro-inflammatory cytokines [37]. One notable effect of a diet high in fat is the resulting state of high adiposity. This increases total body adipose tissue and is a better indication of inflammation than BMI [37]. Increased adiposity leads to the increased production of inflammatory adipokines by the tissue. Examples of these include high leptin, TNF-a, interleukin-6, and angiotensin, which can cross the BBB and exert their effects. Leptin resistance, for example, is implicated in the amplification of AD pathology because it increases the phosphorylation of tau. Increased leptin levels are sustained secondary to increased adiposity, ultimately leading to leptin resistance, which contributes to pathology [37]. Further, there has been shown to be a decrease of protective adipokines such as adiponectin and Brain-Derived Neurotropic Factor (BDNF) due to high adiposity [37]. A Mediterranean diet high in coconut oil has been recommended in individuals with a genetic predisposition to the disease and those in mild stages of AD progression [38]. This is due to the idea that ketone bodies that provide direct energy to the brain can be obtained from coconut oil in a brain that is failing to metabolize and normally uptake glucose [39].

Oxidative damage and curcumin

During normal metabolism, there is a balance between the spontaneous formation of ROS and the production of antioxidant compounds. ROS are scavenged through enzymatic activity by enzymes like glutathione, catalase, and superoxide dismutases [23]. If this balance is not maintained, damage to critical cellular structures can accumulate, leading to eventual cell death. The brain is especially vulnerable to ROS formation due to its high metabolic demand. Neuronal degeneration from ROS imparted on DNA and mitochondria is evident in AD patients and is one explanation for disease onset [23]. Mitigation of oxidative stress via antioxidants is one strategy in the treatment and prevention of neurodegenerative diseases. Compared to other antioxidants like vitamins E and C, curcumin stands as a predominant candidate for neurological protection based on increased potency as a free-radical scavenger. Animal studies have explored the relationship between the consumption of curcumin and AD. In one study, ten-month-old AD APPSw transgenic mice were administered low (160 ppm) and high (5000 ppm) doses of curcumin for 6-month duration. Oxidized brain proteins were used to determine oxidative damage. When comparing four separate brain regions, the AD transgenic mice given high a high dose of curcumin saw a significantly lower amount of oxidized proteins (46.3%) when compared with AD mice not given curcumin. In the same study, soluble Aβ was considerably lower (43%) in mice given low-dose curcumin than in control groups.

Prevention of Aβ plaque formation has become a target for the management of AD. Vitamin A has shown to be an essential regulator for the aggregation of Aβ. Sufficient dietary status of retinoic acid, the active metabolite of vitamin A, is positively correlated with reduced cognitive impairment in older adults [41]. In animal studies, insufficient retinoic acid levels increased Aβ deposition in cortical blood vessels [29]. Aβ formation is thought to be from both APP C-Terminal Fragments (APP-CTF) and tau protein production. Both of these proteins are processed through phosphorylation by CDK5 kinase. In animal studies, the groups administered ATRA saw a disruption to APP-CTF and tau protein processing due to down regulation of CDK5 activity by ATRA [30].

One possible treatment for AD is exploring the gene expression of proteins that remove Aβ from the brain. Removal of Aβ plaques is accomplished by binding of Aβ to low-density lipoprotein receptor-related protein-1 on cortical capillary endothelial cells and transported across the

BBB into the cerebrospinal fluid [42]. ATP-binding cassette B1 transporter (ABCB1) expresses the transport protein Pgp and has shown to clear Aβ through the BBB [19]. ABCB1 is found on MDR1 genes that contain a vitamin D3 response element that can influence the gene expression of Pgp. In animal studies, Pgp levels were 2.25-fold higher in AD transgenic mice treated pre-plaque (9-weeks old) with vitamin D3 than the control group with a vitamin D3 deficient diet. In the same study, AD transgenic mice that were treated post-plaque (20-weeks) with vitamin D3 had a significant decrease in the amount of soluble human Aβ than the control group of the same age [33].

Prevalence

The frequency of Alzheimer's disease varies significantly by age, ethnicity, and race. According to a prediction study conducted in the United States more than 3.2 million Medicare members over the age of 65 had an AD diagnosis in 2014, with a higher prevalence in women (13.3 percent) than males (9.2 percent). Furthermore, the prevalence rose with age, rising from 3.6 percent in the 65–74 age groups to 13.6 percent in the 75–84 age group and 34.6 percent in the 85–year age group. African Americans had the highest prevalence (14.7%), followed by Hispanics (12.9%), Caucasians (11.3%), American Indians and Alaska Natives (10.5%), and Asian and Pacific Islanders (10.1 percent) [43]. It is possible to reach a conclusion. A meta-analysis conducted by Steenland supports the conclusion that African Americans are at the highest risk of AD incidence (2015). They conducted six distinct population-based investigations in the United States, comparing the AD incidence rate between African Americans (AA) and Caucasians (CC), employing 370 AA patients and 640 CC cases. The estimated AA/CC rate ratio revealed that the AA rate was 64% greater than the CC rate (RR=1.64), with no evidence of heterogeneity. Furthermore [44], assessed the US prevalence of AAs and CCs years 65–90 to be 5.7 percent; the prevalence of AAs years 65–90 was 8.6 percent, compared to 5.5 percent for CCs (prevalence ratio 1.56).

Discussion

This paper aimed to explore alternative options for the management of AD. This included holistic approaches to treatment as well prophylactic methods that could be utilized to delay or prevent the onset in demographics that are high risk for development of the disease, such as those with a genetic predisposition like carriers of APOE4 [17]. Accumulation of Aβ in the brain is noted to be one of the primary contributing factors in the pathogenesis of AD and a primary target for treatment. The aggregation of Aβ is represented by 2 likely mechanisms for familial AD: overproduction of Aβ or faulty clearance of Aβ from the brain [32]. From the results of animal models, it was observed that administration of vitamin D3 had a significant role in the clearance of Aβ and that early intervention was more effective in reducing soluble and insoluble human Aβ. It is thought that vitamin D facilitates the expression of Pgp as an efflux pump to clear Aβ from cortical circulation. These data suggested that for maximum efficacy of vitamin D3 as a protective agent for AD, the administration should start before the initial formation of Aβ plaques [33]. Since Pgp has shown to play a role in Aβ clearance, further investigation into increasing activity or expression could be used as a novel treatment option for AD [32]. Suboptimal RA levels have also been correlated with increased accumulation of Aβ in the cerebral cortex of patients with AD [29]. In animal studies, it was demonstrated that ATRA inhibits the kinase enzyme CDK5 from phosphorylation of tau and TPP-CFT proteins, significant contributors in the formation of Aβ. Although ATRA was effective in this experiment, the mechanism for which ATRA inhibits, CDK5 is still unknown [29].

The discrepancy in AD prevalence across various ethnic backgrounds may give insight into disease pathogenesis and possible preventive measures. Cultural practices, like the frequent addition of curcumin in food staples, may create long-lasting protection for cognitive impairment. Neurodegenerative diseases like AD and Parkinson's disease (PD) have a reduced prevalence in India, a country where up to 200 mg of curcumin is consumed daily. A common denominator seen in the pathogenesis of AD and PD is the accumulation of oxidative damage from ROS. Curcumin has been extensively proven to be an effective antioxidant, anti-inflammatory, and anti-apoptotic polyphenol with the capacity to neutralize ROS. Administration of low-dose curcumin in laboratory animals showed a significant reduction of cytokine IL-1β inflammatory markers as well as Aβ [26]. Although high-dose curcumin also showed significant neuroprotective properties, there was no significant increase in protection seen when compared to the low-dose curcumin group. Curcumin, with its relatively low toxicity and potent anti-inflammatory properties, makes it a good candidate as a prophylactic in the prevention or treatment of AD [26].

These are not curative options for the disease as none currently exist [11]. Current allopathic treatments were investigated as both treatments are often used in conjunction [11]. While these holistic treatments showed positive outcomes, it is important to consider that most of the tested populations consisted of AD patients with mild symptoms. Similarly, animal models looking specifically at one hypothesis and studying rare AD gene variants do not capture the multi-factorial disease pathophysiology of AD [29]. Therefore, it is unknown how much of a benefit these approaches will have in a patient who has progressed to severe disease [15]. Studies show that holistic practices only show minor improvements in mild disease, so their effects will likely be negligible once the disease has progressed [15].

Further, many of the studies looking at holistic approaches used samples of patients that were open to treatments and willing to participate; this does not necessarily include the entire population of people living with AD [35]. Since depression is a hallmark feature of the disease and considered the most common associated neuropsychiatric symptom, it is likely that the population of willing participants was reduced secondary to depression-associated apathy and lack of motivation [40].

While we did explore previous research for alternative and holistic methods to treat AD, nothing curative was found. Just like allopathic methods, holistic remedies are only helpful for specific symptoms or specific aspects of a disease with multiple nuances [35]. Once a patient is diagnosed with AD, progression is inevitable; the methods discussed were only useful in mildly slowing progression.

Conclusion

The pathophysiology of AD is complex and has many facets that lead to disease. Current pharmacological treatments can only manage symptoms, and cannot prevent the decline of neurocognition and motor function. Cholinesterase inhibitors such as donepezil, rivastigmine, and galantine increase the amount of acetylcholine in synaptic clefts and are first-line treatments for symptomatic relief. Memantine, an NMDA antagonist, can also be used for symptomatic relief in advanced AD. The use of NSAIDs, specifically diclofenac, has also been indicated to be beneficial and neuroprotective. However, these allopathic options are mostly insignificant, especially as the disease progresses. Because of this, it is essential to use other holistic treatments along with pharmaceutical treatment to maximize symptomatic relief and slow down cognitive decline. Among these alternative treatments, exercise, diet, and turmeric have shown promising results in mild disease. It has been well documented that insufficient dietary vitamin A and D are contributing factors in cognitive impairment in older adults. Animal studies show confirming evidence that adequate vitamin A and D status can reduce the burden of Aβ formation as well as increase Aβ clearance. Conversely, suboptimal levels can enhance the pathogenesis seen in AD. Since the toxicity for both vitamin A and D are well established, they are good candidates for evaluation in clinical trials. Variations seen in AD prevalence across different ethnic groups could be influenced by cultural practices. Curcumin, the orange spice found in a range of Indian cuisines, may have a greater impact on health than we currently understand. Further investigation should be made into curcumin as a prophylactic for AD and a concurrent treatment in early-onset AD. Ultimately, after decades of research, there is still no definitive cure for AD. The multifactorial nature

of AD pathogenesis, with many aspects still unknown, creates a challenge in target treatments. Future treatment protocol for AD may require a multi-component plan. This plan may include dietary changes such as a Mediterranean diet low in saturated fat and moderate aerobic exercise in conjunction with allopathic medications.

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