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The Epidemiology of Alzheimer's Disease and It's Phyto-Therapeutic Approaches

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Abstract: The most prevalent kind of dementia, Alzheimer's disease (AD), provides a stunning illustration of the link between higher-order cognitive deficits and neurophysiological anomalies. Research on the pathophysiology and etiology of AD has revealed an incredibly complex set of genetic and molecular mechanisms for the disease's progression since the disease was first described in 1906. AD is characterized by much more than just the neuropathological hallmarks of beta-amyloid (Aβ) plaques and neurofibrillary tangles (NFTs). Results linking the neurodegeneration seen in AD to the disease's clinical manifestation and course of therapy are included in this review, with a focus on the pathophysiology of the disease. Herbal-based therapeutic agents have been shown to have long-lasting effects that could safeguard the health of the nervous system, reduce inflammatory responses, enhance cognitive function, provide anti-aging effects in the natural ageing process, and reduce dementia sequelae. Herbal based therapeutic agents offer many benefits and can potentially be used as new generation therapeutics or complementary agents with high compliance, low side effects, and low cost compared to traditional pharmaceutical agents in the battle against AD.

Keywords: Alzheimer's disease, neurodegeneration, phytocompounds, pathophysiology, diagnosis

1. Introduction

Alzheimer's Disease is a complex disease with a diverse pathobiology. The main neuropathologic criteria for diagnosing AD are the presence of β-amyloid deposition and hyperphosphorylated tau accumulation. However, recent discoveries show other crucial cellular and molecular processes play significant pathological roles [1].
Originally, Alzheimer was used to refer to pre-senile dementia. Later, it was used to describe the largest cause of primary dementia, which is senile dementia of the Alzheimer type. Alzheimer's disease, also known as Alzheimer's, is a chronic neurodegenerative disease. It gradually starts and worsens over time. It is responsible for 60-70% of dementia cases. Dementia is a general term for the loss of memory and other cognitive abilities that interfere with daily activities. More than 24 million people worldwide are suspected to have dementia, with the majority of them thought to have Alzheimer's disease [2]. Although AD typically affects adults 65 years of age and beyond, it is also increasingly seen in younger individuals beginning at around 40 years of age [3]. According to estimates, one in twenty adults over 65 (up to 35 million in 2015) may experience AD, and beyond age 65, the risk increases about every five years, potentially affecting one-third of all adults 85 years of age or older [4][5].
The pathogenesis of AD is known to be initiated by protein aggregates misfolding, aggregating, and accumulating in the brain. The hallmarks of AD include the following neuropathological indicators. These are the following:

- Amyloid- β extracellular plaques
- Neurofibrillary tangles within cells
- inflammatory response
- disruption of synaptic function
- loss of neurons [6]

These result in oxidative stress biomarkers and alterations in mood and cognition. However, biomarkers for mood and cognition are easily tested. Ten biomarkers (symptoms) for Alzheimer's disease
1. Memory loss that impairs everyday living.
2. Challenges in planning or addressing challenges.
3. Having trouble doing activities you know.
4. Not knowing where or when to go.
5. Difficulty comprehending spatial connections and visual pictures
6. New issues with words while writing or speaking
7. Misplacing objects and losing the capacity to retrace steps.

8. Decreased or bad judgment.
9. Retreating from social or professional engagements.
10. Shifts in personality or mood [7]

Epidemiology and Etiology

The intricate and diverse pathophysiology of Alzheimer's disease is still being investigated, but the genetic, environmental, and societal variables that contribute to the development of this neurological deterioration have received a lot of attention. The primary risk factor for the development of Alzheimer's disease is thought to be aging; only 1-6 percent of cases are early-onset AD (EOAD), which is defined as beginning between the ages of 30-65. In the United States, there are currently around 6.5 million instances of late-onset AD (LOAD), with a predicted increase to 13.8 million cases by 2065. LOAD is far more frequent than AD [8]. While there are numerous studies on the prevalence of AD, there are limitations to these estimates, such as age stage, point at which the pathological process begins, and definition of non-AD patients [9]. In some epidemiological studies, the inferences and estimates were not as precise due to significant statistical variability. However, the existing studies serve as a starting point for new epidemiological studies on preventive and disease-modifying interventions, and therapeutic approaches in AD, and some key predictions and implications remain relevant [10-13]. The influence of social and environmental factors such as exposure to pollutants/toxins, access to health care, and quality of education have led to documented increases in risk-modifying conditions for many diseases, including cardiovascular disease, diabetes, and depression [14].

It is estimated that more than 50 million people worldwide have Alzheimer's disease, and this number is increasing significantly. this increase is largely due to population growth and an increase in life expectancy, as well as improved methods of detecting and diagnosing Alzheimer's disease (especially in less developed countries and poor communities in the United States) [15].

The most studied risk factor for the development of AD is the presence of certain deterministic or predisposing genes; in fact, studies show that the heritability of AD is 50% or more[16]. Genome-wide association studies have so far identified a number of such genes, many of which are directly related to the aforementioned amyloid hypothesis. The first of these is APP, which encodes the amyloid precursor protein. By 2020, 30 mutations had been identified in this gene, 25 of which caused overproduction and accumulation of Aβ42 as a result of changes in the amino acid composition of the APP cleavage site [17]. Mutations in the PSEN1 and PSEN2 genes, whose protein products are involved in the activation of the γ-secretase complex, are also considered to be causally related to the development of AD [18]. However, the most important genetic risk factor is the ε4 allele of the Apolipoprotein E (ApoE) gene, which is present in about 40% of AD patients [19]. The ability of risk factors to modulate each other can be seen in the fact that HSV-1 DNA has been detected in the brains of individuals carrying the ApoE-ε4 allele, an infection of which is an established risk factor for AD [20].

Other well-established factors that modify the risk of developing AD include intelligence and educational level; Although some suggest that these characteristics may actually reduce the incidence of neural damage associated with AD, most favor a framework (the cognitive reserve hypothesis) in which extensive early brain development allows cognitive function to be preserved in the face of this damage [21]. In addition to these factors, many lifestyle factors such as diet, physical activity, brain damage and cardiovascular health are statistically correlated with late-onset dementia [17], but the relationship between these factors and specific Alzheimer's disease is unclear and requires further study. . However, there is substantial research on the role of stress in the development of AD pathology, particularly in relation to the role of corticotropin-releasing hormone signaling in Aβ and tau deposition and neurodegeneration [22].

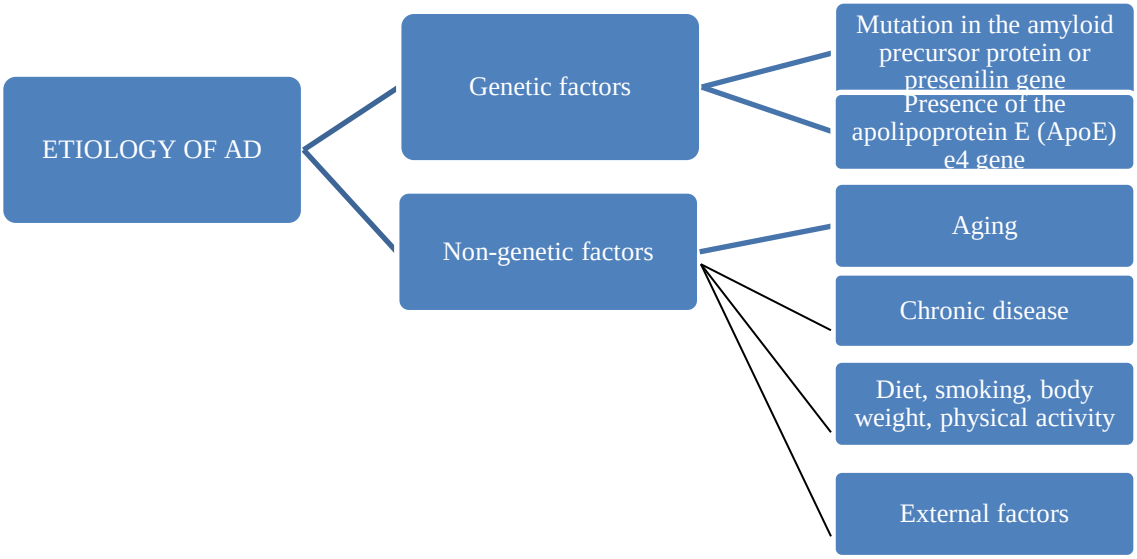

Fig 1:- Schematic presentation of genetic and non-genetic factors involved in the etiology [23]

AD results from significant structural and functional damage to the central nervous system. Two distinct histological lesions have been identified in the etiology of AD: amyloid plaques and NFT (Neurofibrillary tangles). NFT formation begins in the inner part of the temporal lobe. Damage to these hippocampal structures can even occur when a person has no symptoms of cognitive decline. The NFT then develops in the external temporal lobe before spreading to posterior cortical association areas and throughout the cortex [24]. This topography of lesions corresponds to the development of AD symptoms [25]. On the other hand, unlike the NFT topography, thedistribution of amyloid deposits is more irregular. In fact, they are found first in the neocortex, then in the hippocampus, cortical nuclei, and finally in the cerebellum [26].

Conventional Approaches to Ad

Although it's controversial to use the term conventional treatment (because this radical treatment isn't presently available), there are certain groups of medicines that have been involved in the characteristic treatment of announcement for numerous times. In addition to these, there are promising new curatives that are still in the trial phase, but their safety and efficacy have not been proven.

Table 1. Limitations of conventional treatment approaches in AD [23]

S. No.	Current Treatment, Modalities in Alzheimer's Disease	Limitations and Failures in Treatment
1	Acetylcholinesterase Inhibitors	It is not effective in all patient populations, may cause severe gastrointestinal adverse reactions, sleepiness, insomnia, and heart rhythm problems. Clinical efficacy varies between moderate to severe AD and mild AD.
2	Memantine	There are inadequate data on the long term safety and benefit of starting memantine remedy
3	Immunotherapy	The definitive results of the use of immunotherapy in AD haven't been exposed and certain immunization assessments couldn't be tested in humans
4	Antipsychotics and antidepressants	Some of this group of drugs can exacerbate AD sequelae. Treatment may be interrupted due to drug interactions

		Only moderate results can be obtained with antipsychotic group drugs.
5	Statins	Only certain lipid lowering drugs can give results in treatment
6	Vitamin supplements	Antioxidant supplements have not been associated with reduced incidence of dementia in asymptomatic individuals

Novel Phyto-Therapeutic Approaches

Plant bioactive compounds are plant-derived components containing pharmacologically active molecules. They are known as 'herbal medicinal' products. These plant-derived compounds are superior to synthetic drug molecules in many ways. This is because they have the ability to bind to a wide variety of target sites in cells and tissues and have many types of pharmacological activity. Their structures have many voids and are easy to produce [27,28]. AChEI, the most commonly used symptomatic treatment for AD, causes side effects such as nausea, vomiting, and appetite disorders due to severe bowel movements [29]. On the other hand, phytopharmaceuticals are safer and have fewer side effects, which may make them an ideal option, especially for patients with multiple chronic diseases. The balance of ions such as Cu^{2+}, Zn^{2+}, and Fe^{2+} in the brain is crucial for the maintenance of physiological processes [30,31].

Table 2. Phyto-therapeutic treatment approaches in AD

S. No	Plant bioactive compounds	Treatment
1	Resveratrol	A polyphenol which exhibited neuroprotective effects by reducing oxidative stress and protecting the brain against memory impairment and hippocampal damage. It is a treatment choice for patients with hypertension who are in danger of AD in old age. The potential of resveratrol to be used in neuroinflammation-related diseases like Alzheimer's disease (AD) was emphasized. The study looked at the protective effects of resveratrol on neuroinflammation and cognitive deficits caused by lipopolysaccharide (LPS) in rats.[32]
2	Tannic Acid	It is a hydroxybenzoic acid which has anti-amyloidogenic and fibril-destabilizing activity.[33] Orally administrated TA worked on mental capabilities and forestalled conduct decay in a transgenic mouse cerebral amyloidosis model for six. By inhibiting secretase activity and neuroinflammation, it was determined that TA treatment alleviated AD pathology and amyloid deposits.[34]
3	Apigenin	Important neuroimmunomodulator in the treatment of AD. Apigenin in AD neurons was displayed to decrease neuronal hyper-excitability and apoptosis, as well as shield from neuronal harm and demise with its anti-inflammatory. [35]
4	*Psoralea corylifolia* L.(bavachin, bavachinin, bavachalcone, and isobavachalcone)	Neuroprotective compound [36]
5	Curcumin	Prevents oxidant damage with its antioxidant activity, regulate the cellular signaling pathway and prevent Aβ from forming β-layer aggregation and neurotoxicity [37]
6	Rutin	Restore microglial phagocytic capacity and promote Aβ clearance, reduce neuroinflammation, and improve learning and memory deficits [38,39]
7	Quercetın	Protective role by reducing oxidative stress, inhibiting AChE, and increasing cognitive and behavioral functions [40]

8	Caffeic Acid	Improves learning and memory as well as antioxidant, anti-apoptotic, and anti-inflammatory activity [41]
9	Hesperidin	Reduce AChE activity, suppress Aβ accumulation by suppressing β- and γ-secretase expression and reverse learning and memory impairments [42]

2. Conclusion:

Alzheimer's disease has gained recognition as a global health issue. Consequently, the National Institute on Aging—Alzheimer's Association has revised and enhanced the 1984 NINCDS-ADRDA criteria. These updates aim to improve the accuracy, sensitivity, and early detection of individuals who are susceptible to developing AD. Multiple research studies have demonstrated that making changes to one's lifestyle, particularly in terms of diet and physical activity, can enhance brain health and mitigate the progression of Alzheimer's disease (AD) without the need for medical intervention. This approach is widely regarded as the primary intervention for all individuals diagnosed with AD. Presently, scientific investigations are primarily centered around addressing the pathological characteristics of AD, including Aβ and p-tau. This review examines the neuropharmacological mechanisms of phytochemicals that exhibit preventive and therapeutic effects in Alzheimer's disease, a prevalent and highly incident neurodegenerative disorder. The neuroprotective mechanism of natural products utilized in different cell and animal experimental models specific to AD is believed to involve enhancing endogenous antioxidant defense functions and suppressing neuro-inflammatory and apoptotic pathways.

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