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Alzheimer's Disease and Role of Medicinal Plants

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ABSTRACT

An Alzheimer's disease is a progressive, degenerative disease of the brain that leads to dementia, that majorly characterized by nerve cell helical protein filaments. The global burden of AD is expected to accelerate from 16.6 million cases in 2006 to 106.8 million by 2050. Alzheimer's diagnosis can include clinical exam, MRI and/or CT scan and the amyloid beta, pathological Tau proteins are the core markers. Mainly, three drugs approved for the treatment of mild to moderate AD are donepezil, rivastigmine and galantamine. Reuptake inhibitors like fluoxetine, sertraline, fluvoxamine are largely considered to treat comorbid depression in AD dementia. Apart from the few available allopathic medications, some of the medicinal plants like *Centella Asiatic*, *Rhodiola rosea* -salidroside, the Silk Protein-Sericin, *Centella asiatica*, *Clitoria ternatea*, *Crocus sativus*, *Terminalia chebula*, *Withania somnifera*, and *Asparagus racemosus* are proved to show ant Alzheimer's activity based on the available phytoconstituents especially plant choline's. In this review, we will discuss about Alzheimer's disease and the reported actives of some plants to focus the attention of neurological research on demand of exploring ant Alzheimer's disease.

INTRODUCTION:

An Alzheimer's disease is a progressive, degenerative disease of the brain that leads to dementia. Alzheimer's disease (AD) is majorly characterized by nerve cell helical protein filaments. It is a specific disease that affects about 6% of the population aged over 65 and its incidence increases with age . India occupies the third highest Alzheimer's caseload across the world, after China and the US with the prevalence range of about four millions. The global burden of AD is expected to accelerate from 16.6 million cases in 2006 to 106.8 million by 2050 [10] (Ferri CP *et al.*, 2015).

Alzheimer's affects almost 15 million people worldwide. AD induced dementia will worsen the life of elders. Disturbances, like aggression, urination, and excessive wandering, are a major source of caregiver burden that makes the patient to go for institutionalized long-term care. The social and psychological skills and the compliance of the caregivers, as well as the presence and competence of the social networkers, determine to a large extent whether a demented patient with behavioural problems can live at home or needs nursing home admission [3] (Exp Gerontol *et al.*, 2001).

Psychological symptoms and behavioural abnormalities are common and prominent characteristics of dementia. There are complex interactions between cognitive deficits, psychological symptoms, and behavioural abnormalities. A large number of standardized, reliable, and well-validated instruments for assessing the behavioural and psychological symptoms of dementia have been developed now-a-days.

SYMPTOMS:

With the cognitive decline in Alzheimer's Dementia (AD), the frequentness of neuropsychiatric symptoms increases. Mild stage of AD will have affective symptoms whereas moderately impaired cognition shows agitated and psychotic behaviour. Based on nature of symptoms Alzheimer's disease are majorly of two types.

- Cognitive symptoms

It includes memory loss, language difficulties, and executive dysfunction.

- Non- Cognitive symptoms

The non-cognitive symptoms include both behavioral and psychiatric symptoms.

- Behavioral symptoms

Aggression, agitation, disinhibition, restlessness, wandering

- Psychological symptoms

Anxiety, depressive mood, hallucinations and delusions, apathy

DIAGNOSIS:

Role of the diagnostic work up of Alzheimer includes clinical exam, medical history of the patient, assessment of multiple cognitive domains, lab tests, MRI and/or CT scan, in some cases. Through Magnetic resonance imaging, positron emission technique, and cerebrospinal fluid analysis technique, distinct and consistent biomarkers of AD are analysed. The clinical diagnoses of AD include, firstly history of the patient. Secondly, evaluation of mental state and confirmatory cognitive function tests. Physical examination is also useful. Assessment of dementia includes differentiation of dementia from other conditions like depression, delirium, and mild cognitive impairment.

BIOMARKERS FOR AD:

Biomarkers are physiological, biochemical, anatomical variables that can be measured *in-vivo* and that indicate specific features of disease-related pathological changes. They are the important evidences to determine the underlying pathophysiology of the disease. The reliable biochemical markers such as Amyloid beta and pathological Tau proteins are the core components of amyloid deposits and neurofibrillary tangles, respectively (Clifford R Jack., 1010). Some of the imaging and CSF biomarkers in AD are Brain Amylod beta deposition biomarkers are CSF $A\beta_{1-41}$, PET Aβ imaging Neurodegeneration, CSF tau, Fluorodeoxyglucose PET [8] (*Lancet* Neurol *et al.*,2010).

Risk Factors:

Risk factors for vascular dementia were divided into three major classes.

The major atherosclerotic risk factors were important in cases with history of hypertension, cigarette smoking, myocardial infarction, diabetes mellitus, and hyperlipidaemia (Ilaria Di

Donato., 1017). The genetical important factors included cerebral autosomal dominant arteriopathy with subcortical infarct, leukoencephalopathy and possibly apolipoprotein (apoE)4 [6](Nat Rev Neurol *et al*., 2013).

- **Age**

Geriatrics will have more chances of incidence of AD than younger ones. As the age progress, the decreased neuronal functioning will increase chances of AD.

- **Gender**

No consistent evidence was seen regarding the incidence of AD, but in females due to the hormonal imbalance the incidence of AD may be more.

- **Family history**

In case of first-degree relatives, the risk for incidence of AD was 3.5-fold more. Based on the studies, the concordance is higher in monozygotic twins than in dizygotic twins, indicating the presence of a genetic component.

- **Mutations**

Mutations was majorly seen in three genes, that is the amyloid precursor protein, presenilin 1, and presenilin 1. ApoE located on chromosome 19, is the genetic risk factor for the incidence of late onset AD. ApoE exist in three forms ApoE e1, ApoE e3, and ApoE e4.

- **Environmental Factors**

The importance of environmental factors is confirmed by the fact that the strongest association is not true across all races and 50% of white patients with Alzheimer's disease.

- **Co-morbid conditions**

Head injury, depression, hypertension, diabetes, high cholesterol, atrial fibrillation, presence of cerebral emboli, low physical and cognitive activities are some of the risk factors.

PATHOPHYSIOLOGY OF AD:

Clinically AD divided into three phases.

- First stage is a pre-indicative stage in which people are psychologically typical yet some have AD obsessive changes.

- Second is a prodromal period of AD, regularly alluded to as gentle subjective weakness (MCI), which is described by the beginning of the most punctual intellectual indications. The seriousness of psychological hindrance in the MCI period of AD changes from the soonest appearance of memory brokenness to progressively boundless brokenness in other intellectual spaces [18] (Marilyn S. Albert *et al*., 2011).

- The last stage in the development of AD is dementia, characterized as disabilities in different areas that are sufficiently extreme to create loss of capacity. Neuronal loss and/or pathology may be seen particularly in the hippocampus, amygdala, entorhinal cortex and the cortical association areas of the frontal, temporal and parietal cortices, but also within subcortical nuclei including serotonergic dorsal raphe, noradrenergic locus coeruleus, and the cholinergic basal nucleus.

The deposition of tangles follows a defined pattern, starting from the trans entorhinal cortex, consequently the entorhinal cortex, the CA1 region of the hippocampus and then the cortical association areas, where frontal, parietal and temporal lobes are particularly affected. The extent and placement of tangle formation correlates well with the severity of dementia [1] (Alberto Serrano-Pozzo *et al*., 2011).

The increases tau protein effect the cognitive decline and brain atrophy, including hippocampal atrophy. In the neuropathology of Alzheimer's disease there is a loss of neurons and atrophy in temporofrontal cortex, which causes inflammation and deposit the amyloid plaques, forms an abnormal cluster of protein fragments and tangled bundles of fibers due to this there is an increase in the presence of monocytes and macrophages in cerebral cortex, it also activates the microglial cells in the parenchyma [20] (Mishra S., 2008). The activated glia and of glial cytokines play a role in the pathogenesis of Alzheimer's disease Interleukin-1 (IL-1). Interleukin-1 upregulates articulation, handling of β-amyloid antecedent proteins and actuates articulation of α1-antichymotrypsin, thromboplastin, the supplement protein C3, apolipoprotein E, in the neurotic plaques.

These cytokines, the molecular and cellular events, form a complex of interactions that may be capable of self-propagation, leading to chronic overexpression of glial cytokines with neurodegenerative consequences. *β*-Amyloid, for instance, directly activates microglia, thus inducing more IL-1 production, or activates the complement system, which also leads to microglial activation with IL-1 expression. Such chronic, self-propagating, cytokine-mediated molecular and cellular reactions are the result of progressive neurodegeneration and dementia of Alzheimer's disease [5] (Robert E. Mark., 1995, 1996).

In AD, these progressions happen in the hippocampus, Para hippocampal gyrus, parietal projection, retro splenial cortex, prefrontal cortex, and caudate core, while in maturing, changes happen for the most part in the prefrontal cortex and the hippocampus. The route capacities of patients with gentle intellectual hindrance (MCI) will show distinctive execution designs, contingent upon their subjective profiles. Since patients with MCI do not uniformly develop dementia of the Alzheimer type, it is important to identify reliable early cognitive markers of conversion to AD dementia.

Hyperphosphorylated tau protein and amyloid β speculation:

One of the primary obsessive highlights of AD is the development of decrepit plaques (SP), which is brought about by amyloid beta (Aβ) statement. Ordinarily, Aβ are dissolvable little peptides, which are delivered by the parting of the antecedent protein of amyloid (APP) by the activity of α-secretase, β-secretase and γ-secretase. The lop-sidedness between β- amyloid (Aβ) creation and freedom prompts different kinds of harmful oligomeric, to be specific protofibrils, fibrils and plaques relying on the degree of oligomerization. The explanation of the arrangement of Aβ is as yet hazy, yet the succession, focus and states of dependability of Aβ are significant elements [4] (C. Cheignon., 2018).

Oxidative pressure speculation:

Mitochondrial brokenness assumes a significant job in AD, where oxidative pressure actuated respiratory chain brokenness, loss of mitochondrial biogenesis, imperfections of mitochondrial elements and mtDNA changes are seen. In AD, there are various contributory sources that are thought to assume a significant job in free extreme creation. Initially, Iron, in a redox-dynamic state, is expanded in NFT just as in Aβ stores (Catherine A Rottkamp *et al*., 1001). Iron catalyses the development of OH from H1O1 just as the arrangement of cutting

edge glycation final results. Besides, aluminium, which likewise collects in NFT-containing neurons, invigorates iron-initiated lipid peroxidation.

Microglia, those that encompass most feeble plaques, are a wellspring of NO and O1− that can respond to shape peroxynitrite, leaving nitro tyrosine as a recognizable marker. The Aβ, itself, has been straightforwardly involved in responsive oxygen arrangement through peptidyl radicals. Propelled glycation final results within the sight of change metals can experience redox cycling with subsequent creation of responsive oxygen [12](Hachinski V. *et al.,* 1994).

Furthermore, propelled glycation final results, just as Aβ, enact explicit receptors, for example, the receptor for cutting edge glycation final results (RAGE) and the class A scrounger receptor, to increment responsive oxygen creation. Variations from the norm in the mitochondrial genome, or inadequacies in key metabolic proteins recommend that metabolic anomalies influencing mitochondria might be the major, and perhaps starting, wellspring of responsive oxygen in AD.

Responsive oxygen species (ROS) and receptive nitrogen species (RNS) are created in different cellular occasions in people, that assumes a job in cell flagging pathways and may prompt harm of some cell structures. Cerebrum requires 10% more oxygen and at some point, defenceless against oxidative pressure. The neuron is the essential practical unit of the mind, which contains countless polyunsaturated unsaturated fats. It can communicate with ROS, prompting the lipid peroxidation response and sub-atomic apoptosis, what's more, less glutathione in neurons is additionally one of the reasons for oxidative pressure injury. The utilization of cancer prevention agents can forestall the nerve harm delivered because of oxidative pressure [21] (Uttara B *et al*., 2007).

Metal ion hypothesis:

Metal ions are involved in the progression and pathogenesis of diseases, including neurodegerative diseases and cancer. Ionosphere and metal chelators are completely known modulators of transition metal homeostasis, and a number of these molecules are used in clinical trials. Metal binding compounds are not the only drugs capable of targeting transition metal homeostasis [7] (Claire M Weekly *et al*., 1018) Current evidences indicate changes in the equilibrium of redox transition metals, majorly copper (Cu), iron (Fe) and other trace metals. These metal ions are found to be high in AD patients.

Cholinergic hypothesis:

AchEI medications are the important part of the treatment of AD, and APOE genotype is one of the most important factors associated with AD. Cholinergic receptor binding is reduced in specific regions of brain that relates to neuropsychiatric symptoms and also reveals changes associated with aging, AD and may provide a potential molecular treatment target [11] (Talita H. Ferreira-Vieira *et al*., 1016).

Metals:

Lithium a neuroprotective, will modulates several homeostatic mechanisms involved in neurotrophic response, autophagy, oxidative stress, inflammation, and mitochondrial function. Intracellular responses may include the inhibition of glycogen synthase kinase-3 beta (GSK-3β) and inositol monophosphatase (IMP) by lithium.

ncRNAs like circular RNAs, piRNAs and lncRNAs are also involved in AD. Non-coding RNAs may become useful biomarkers for AD and targets for treatment. Neuroinflammation and oxidative pressure; variant age of β-amyloid-41 (Aβ41), abnormalities in the creation, cleavage and post-translational stamping of Tau, impeded freedom of Aβ41 and Tau, irritation of axonal association, interruption of synaptic versatility, endoplasmic reticulum stress and the unfurled protein reaction, neurons mitochondrial brokenness, distorted enlistment of cell cycle re-emergence, and apoptotic loss of neurons [2](Mark J Millen., 2017).

Treatment:

Generally, the cholinergic hypothesis of AD concludes that cholinergic systems in the basal forebrain are affected early in the disease process, including loss of acetylcholine neurons, loss of enzymatic function for acetylcholine synthesis and degradation, resulting in memory loss and deterioration of other cognitive and noncognitive functions such as neuropsychiatric symptoms [9] (Bertus *et al*., 1981).

Mainly, three CIs approved for the treatment of mild to moderate AD are donepezil, rivastigmine and galantamine [14] (Farlow *et al.*,, 2001). Donepezil and rivastigmine are commonly used in all types of Alzheimer's. Rivastigmine was used as transdermal patch.

NMDA antagonist contains one lonely member, memantine. Memantine's individual mechanism of action require improvement of the brain's sensitivity to an important excitatory amino acid neurotransmitter, glutamate. Memantine's side effects are frequently minimal, sometimes through memantine can enhance or initiate confusion, agitation, constipation, or headache [13] (Ho SC, Liu JH, Wu RY *et al.*, 2003).

Reuptake inhibitors like fluoxetine, sertraline, paroxetine, citalopram, fluvoxamine are largely considered to be among the most efficient antidepressants to treat comorbid depression in AD dementia [15](Zec and Burkett *et al.*,*2008*).

Lately, the primary focal point of research on novel pharmacotherapies depended on the amyloidogenic theory of AD, the beta amyloid (Aβ) peptide is mainly answerable for psychological weakness and neuronal demise [16](Korczyn AD).

The objective of Alzheimer's pharmacotherapy is to diminish Aβ creation through the restraint of β and γ secretase chemicals and to advance disintegration of existing cerebral Aβ plaques. Inhibition of the downstream Aβ signalling, particularly at the synapse Aβ oligomers may cause abnormal N-methyl-D-aspartate receptor (NMDAR) enactment postsynaptically by shaping buildings with the phone surface prion protein (PrPC). PrPC is advanced at the neuronal postsynaptic thickness, where it cooperates with Fyn tyrosine kinase. Fyn trigger occurs when Aβ is bound to PrPC-Fyn complex. Fyn causes tyrosine phosphorylation of the NR1B subunit of metabotropic glutamate receptor. Fyn kinase blockers masitinib and saracatinib have demonstrated to be solid in rewarding AD indications in trial mouse models of the malady [19] (Jaume Folch *et al.*, 2016).

Reported Activities of Ant Alzheimer Medicinal Plants:

J Nat *et al.*, investigated the phytochemical bioactive compounds of the ethanolic extract of leaves of *Centella Asiatic.* Evaluated the antioxidative, AChE inhibitory and anti-diabetic activity. Based on the findings, he stated *Centella asiatic* possessing alkaloids, flavonoids, steroids were effective in the treatment and management of Alzheimer Disease and Diabetes [17] (J Nat *et al.*, 2011).

Jin jao *et al.*, had evaluated the preventive effects of salidroside (sal) on a rat model of Alzheimer's disease and planned to explore its possible mechanism. Sub-acute maturing was instigated in male rodents by subcutaneous infusion of D-lady (110 mg/kg) for 41 days, and

the rodents were treated with Sal (10, 40 mg/kg) or typical saline for 18 days following 14 days of D-lady infusion. Morris water labyrinth and venture down latent shirking tests can improve intellectual limit by repressing neuroinflammation and influencing apoptosis-related proteins in hippocampus [22] (Wang Z. *et al.*, 1999).

The natural Silk Protein, Sericin, was screened for "Cognitive enhancer" activity in AD-induced rat model. Sericin could effectively reverse the AD-induced damage in neurons of CC and HC regions, and can be used as a potential cognitive enhancer in general and AD [23] (Yellama K., 2014). Plant alkaloids are one of the most divorce groups of secondary metabolites found in living organisms and have an array of structure type, biosynthetic pathway, and pharmacological activities. Although alkaloids have been traditionally isolated from plants an increasing number are to be found in animals, insects, marine invertebrates and microorganisms. Many alkaloids have been used for hundreds of years in medicine and some are still prominent drugs today [24] (Zakaria, M. *et al.*,1991).

Some of the medicinal plants useful in Alzheimer's include Ginkgo *biloba, Withania somnifera, Bacopa monnieri, Salvia officinalis, Melissa officinalis, Tinospora cordifolia, Glycyrrhiza glabra.*

CONCLUSION:

As the global burden of AD is expected to accelerate every year, research should be focused on investigating of medicinal plants with Anti-Alzheimer's potential, so the elderly persons with dementia can be supported in the last part of their life with the medications to have a peaceful struggleless life. The therapeutics of plant origin can be extremely useful with fewer side effects than the synthetic allopathic medications.

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Conflict of interests:

The authors declared no conflict of interest.

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