ECONOMIC AND SOCIAL IMPACT TO ALZHEIMER'S AND ITS THERAPEUTIC INTERVENTIONS

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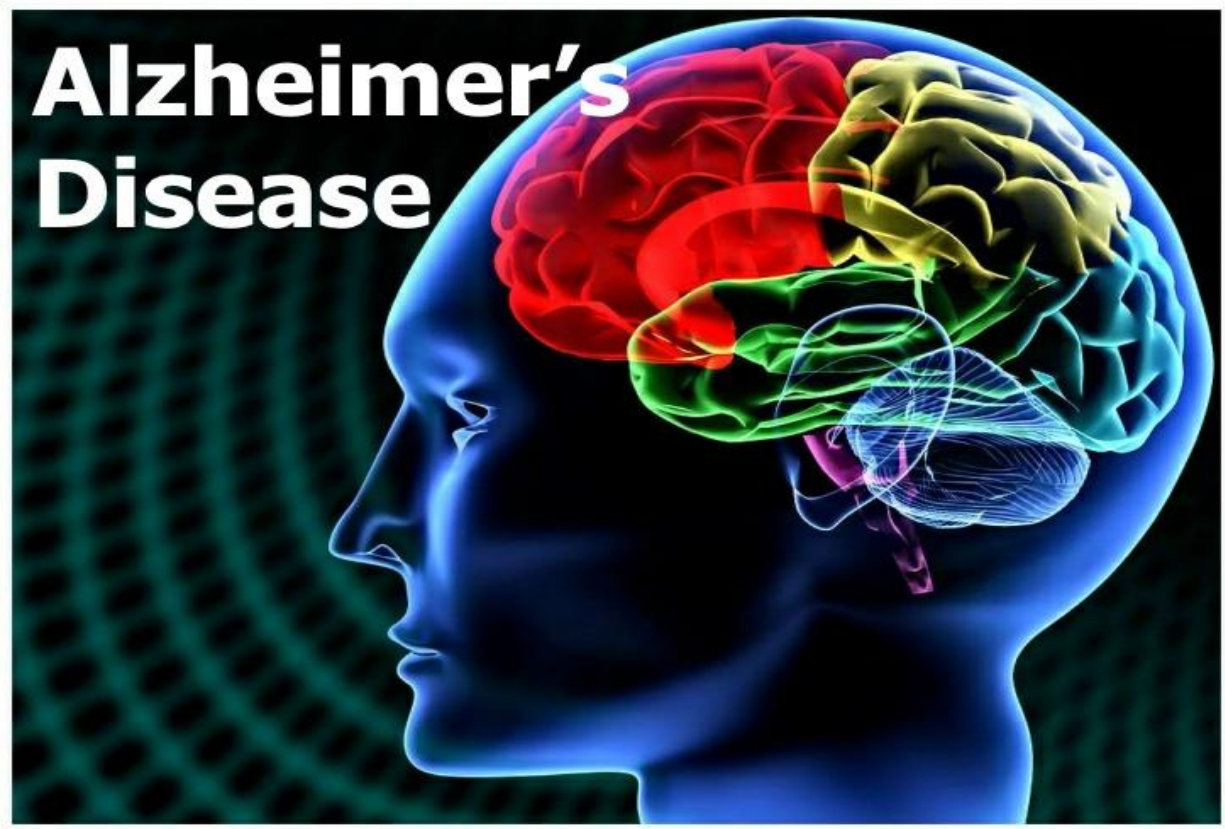
❖ Abstract :-

Alzheimer's disease (AD) is a progressive neurodegenerative disorder marked by irreversible memory loss, cognitive decline, and linguistic impairment, primarily affecting the elderly. Characterized by extracellular amyloid beta (Aβ) plaques and intracellular hyperphosphorylated tau protein tangles, AD is the most common form of dementia. Cognitive impairment in AD is largely due to the decline of acetylcholine (ACh) levels from cholinergic neuron degeneration in the forebrain. Pathogenesis involves amyloid plaque formation, oxidative stress, neuroinflammation, and cholinergic dysfunction. Epidemiologically, AD ranks as the sixth leading cause of death in the U.S., with incidence rates expected to triple by 2050. AD progresses through mild, moderate, and severe stages, significantly impacting daily functioning and quality of life. Key risk factors include age, genetics, and family history, with the APOE ε4 allele being a notable genetic determinant. Current treatments focus on symptom management rather than curing the disease, employing cholinesterase inhibitors like donepezil and rivastigmine to enhance cholinergic function. Curcumin shows potential in preventing tau phosphorylation and amyloid plaque formation. Research continues into anti-inflammatory medications and vaccines targeting amyloid development, offering hope for improved outcomes and quality of life for those affected by AD.

Keyword: Alzheimer's disease including its key characteristics, underlying mechanisms, and diagnostic advancements & epidemiology ,type of dementia in Alzheimer's disease , Pathophysiology and therapy & Benefit of Alzheimer's disease.



INDRODUCTION

Alzheimer's disease, is an irreversible neurological condition primarily characterized by memory loss and cognitive and linguistic impairment. It is brought on by the degenerative loss of neurons in the cerebral cortex. [1]–[2] Alzheimer's disease (AD) is the most prevailing neurodegenerative disease associated with old age, which leads to progressive memory loss and cognitive MG .[3] Intracellular tangles of hyperphosphorylated tau protein and extracellular plaques of amyloid peptide (Aβ) are characteristics of Alzheimer's disease. [4]The decline of cholinergic neurons in the forebrain is another characteristic of AD, and a decrease in the Ach level causes cognitive and memory impairment. [4]–[5] The mechanisms behind AD include the production of inflammatory mediators, a rise in oxidative stress, a decrease in steroid hormones, and the generation of amyloid plaque deposition. [5]

There is strong evidence that progressive biomarker changes occur prior to cognitive impairment genetically at-risk populations & otherwise cognitively normal individuals [6,7,8] The steady build-up of abnormal amyloid beta (Ab) species in the brain [9,10], which begins a decade or more prior to the onset of symptoms, is one significant alteration. Criteria for the clinical diagnosis of Alzheimer's Disease (AD) were established by a National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's

Disease and Related Disorders Association (ADRDA) workgroup in 1984 [11]. These criteria were universally adopted, have been extremely useful. A and have survived intact without modification for over a quarter of a century. In the intervening 27 years, however, important advances in our understanding of AD, in our ability to detect the pathophysiological process of AD, and changes in conceptualization regarding the clinical spectrum of the disease have occurred.

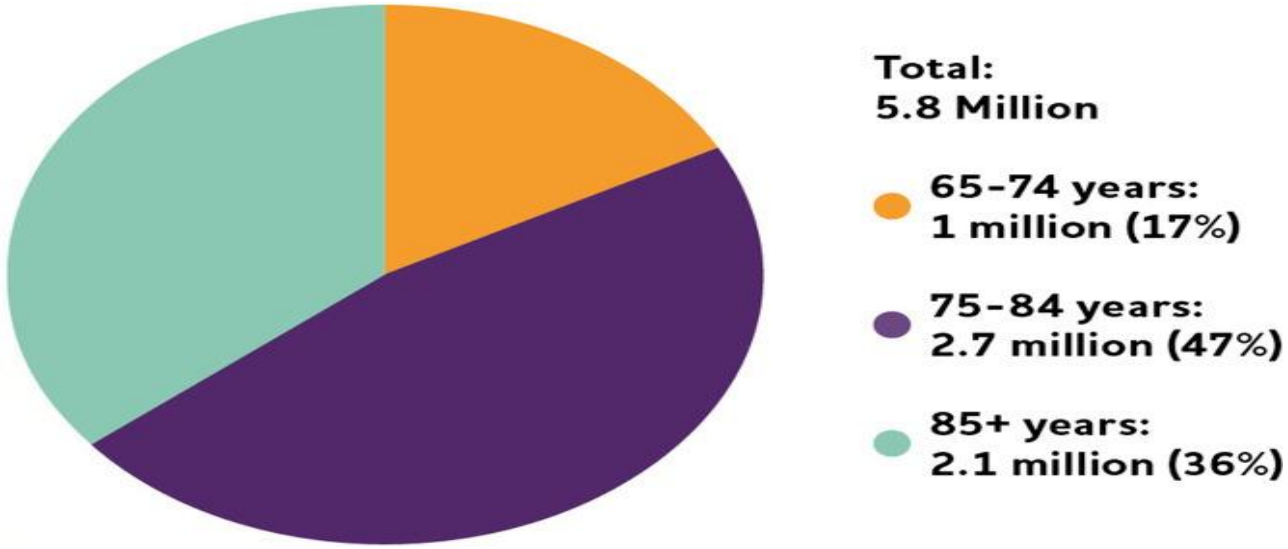
EPIDEMIOLOGY

The most prevalent neurodegenerative illness and the sixth leading cause of mortality in the US is Alzheimer's disease (AD).[7] Considering mounting evidence that AD disease begins to accumulate in the brain in middle age, The onset of clinical signs typically happens beyond the age of 65. [12,13] AD prevalence is rising quickly.

Due in major part to the fact that the proportion of adults 65 and older is growing faster than that of any other age group in the world, the prevalence of AD is rising quickly. The number of people 65 years of age and older, known as the elderly population, is expected to rise from 63 to 137 million in the Americas, from 18 to 38 million in Africa, from 113 to 170 million in Europe, and from 172 to 435 million in Asia between 1997 and 2050. [14,15]

According to the Aging, Demographics, and Memory Study (ADAMS), a nationally representative US data collection, 14% of Americans aged 71 and above are projected to have dementia. Seventy percent of dementia diagnoses in this cohort across all age groups were due to AD dementia.[16]. There have also been reports of racial differences in the prevalence of AD. Compared to older Caucasians, older African Americans and Hispanics have a higher prevalence of AD. This is partly due to lower educational attainment and a higher frequency of cardiovascular comorbidities, while other genetic and sociocultural variables probably also play a part. [17,18]

The most common type of dementia, Alzheimer's disease (AD), is characterized by a decline in behaviour, function, and cognition that usually starts with memory loss related to recent events [19]. The two most important clinical characteristics found in the brain tissues of AD patients are elevated levels of hyperphosphorylated tau (p-tau), and amyloid-β (Aβ), which forms extracellular senile plaques [20]. Around 50 million individuals worldwide suffer from dementia, and as the population ages, it is expected that this figure will quadruple by 2050, increasing the risk of incapacity, the financial burden of sickness, and the expense of medical care [21].



Number and ages of people 65 or older with Alzheimer's dementia, 2020. Created from data from Hebert et al. [22,23]

DEMENTIA DUE TO ALZHEIMER'S DISEASE

Alzheimer's disease-related dementia is typified by observable cognitive, behavioural, or memory problems that affect a person's capacity to carry out daily tasks in addition to signs of brain abnormalities associated with the disease. Many symptoms that vary over years are experienced by people with Alzheimer's disease. The degree of damage to nerve cells in various brain regions is reflected in these symptoms. Each person experiences dementia symptoms differently, ranging from mild to moderate to severe.

MILD ALZHEIMER'S DEMENTIA

mild dementia caused by Alzheimer's Most persons with mild Alzheimer's dementia can function independently in most situations, but in order to optimize their freedom and be safe, they may need support with certain activities. They could still be able to work, drive, and engage in their favourite hobbies. Making financial decisions and paying bills can be particularly difficult. According to the U.S. Social Security Administration, individuals suffering from dementia are more vulnerable to financial abuse and fraud. [24] 5 Declines in executive function can manifest as poor judgment, acting in a socially inappropriate manner, trouble organizing and completing tasks, and an inability to recognize how one's actions or decisions influence other people.[25]

MODERATE ALZHEIMER'S DEMENTIA

The most advanced stage of Alzheimer's disease is known as the moderate stage, during which time a person may experience problems speaking and carrying out everyday activities like dressing and bathing; occasionally become incontinent; and exhibit personality and behavioural changes like agitation and suspicion.

SEVERE ALZHEIMER'S DEMENTIA

People with Alzheimer's dementia who are in the severe stages of the disease typically need 24-hour care and assistance with everyday tasks. At this point, the impacts of Alzheimer's on a person's physical health become more noticeable. Those who suffer brain injury in regions related to movement eventually become bedridden. Due to their bed rest, they become more susceptible to blood clots, skin infections, and sepsis, which can cause organ failure by inciting widespread inflammation in the body. Eating and drinking become challenging when there is damage to the brain regions that regulate swallowing. As a result, people may swallow food into their windpipe, the trachea, rather than their oesophagus, or food pipe. As a result, food particles have the potential to lodge in the lungs and induce lung infections. Aspiration pneumonia is the name of this type of infection, which is a contributing factor in the deaths of many Alzheimer's patients.

RISK FACTORS FOR ALZHEIMER'S DEMENTIA

People 65 years of age or older make up the vast majority of those who get Alzheimer's dementia. We refer to this type of dementia as late-onset Alzheimer's. Experts think that rather than having a single cause, Alzheimer's dementia develops as a result of several circumstances, similar to other prevalent chronic diseases and ailments. There are some exceptions, such as Alzheimer's disease associated with trisomy 21 in Down syndrome and infrequent instances of the disease linked to particular mutations in the genetic code.

AGE, GENETICS AND FAMILY HISTORY

The main risk factors for Alzheimer's disease with a late onset are advanced age [26,27] genetics and a family history of the disease. [27,28]

Age:-

Out of these three risk factors, age is the biggest. As people age, the percentage of those with Alzheimer's dementia rises sharply. According to the Prevalence section on page 22, 5.0% of individuals 65 to 74, 13.2% of those 75 to 84, and 33.4% of those 85 years of age or older have Alzheimer's dementia. The number of Americans suffering from Alzheimer's dementia will rise dramatically as the population ages, especially the baby-boom generation.[29] It is crucial to remember that Alzheimer's dementia is not a typical aspect of aging and that Alzheimer's dementia cannot be brought on by advanced age alone.[30] It's critical to understand that Alzheimer's dementia is not a normal aspect of aging; being years of age or older is not enough to produce Alzheimer's dementia.[31]

MOLECUL BIOLOGY (GENETICS):-

Numerous genes that either raise or lower the incidence of Alzheimer's disease have been discovered by researchers. Indeed, in 2022, scientists discovered 31 novel genes that seem to impact molecular mechanisms implicated in Alzheimer's disease.[32]

For Example , statistics reveal that the proportion of Black and African Americans with at least one copy of the e4 gene is higher than that of European Americans.[33,34] In comparison to inheriting solely copies of the e2 or e3 forms, the chance of acquiring Alzheimer's dementia generally increases with inheriting one copy of the e4 form and increases even further with inheriting two copies of the e4 form.[35,36] Furthermore, compared to people with the e2 or e3 versions of the APOE gene, those with the e4 form are more likely to experience beta-amyloid buildup and Alzheimer's dementia at a younger age.[37]

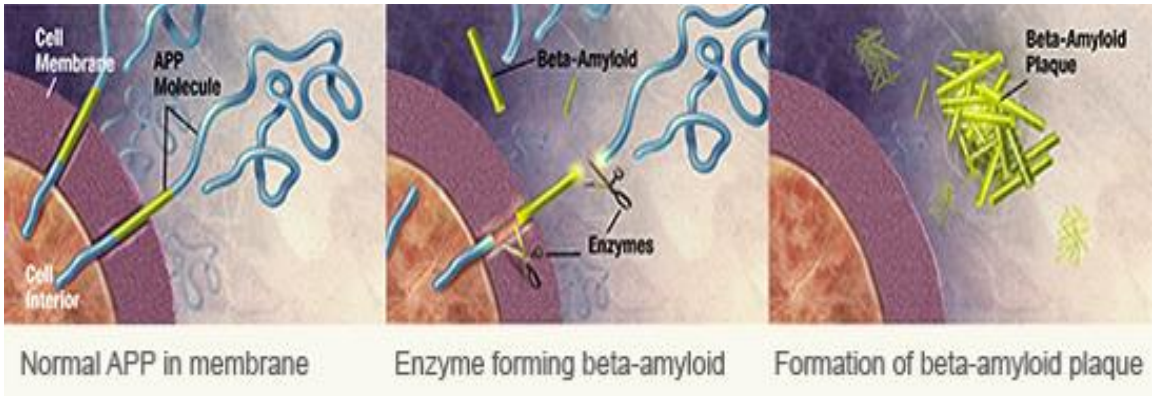
TA B L E : The Share of European Americans and Blacks/African Americans with Identified APOE Pairs

APOE Pair	Blacks/African Americans	European Americans
e3/e3	45.2	63.4
e3/e4	28.6	21.4
e3/e4	15.1	10.2
e 2/e4	5.7	2.4
e4/e4	4.5	2.4
e2/e2	0.7	0.2

Created from data from Rajan et al . [38]

PATHOPHYSIOLOGY OF ALZHEIMER'S DISEASE

AMYLOID BETA PLAQUES :- Amyloid beta peptides (36-43 amino acids), derived from the amyloid precursor protein (APP), are the main components of amyloid beta plaques in AD brains. APP is a transmembrane protein associated with neuronal development. This protein undergoes proteolysis by the beta- and gamma- secretases and releases the amyloid beta peptides. Mutations in the APP gene as well as the PSEN genes lead to the formation of longer amyloid fragments which clump together into oligomers and fibrils[40]. According to recent research, amyloid oligomers—rather than plaques—are the harmful species because they can cause oxidative damage, tau phosphorylation, and synaptic dysfunction. Additionally, it has been shown that amyloid plaque-affected brain regions have decreased neuronal and synaptic damage .[39,41]



The β-and γ-secretase enzymes cleave the amyloid precursor protein (APP) to create the insoluble component amyloid beta, which is essential for the production of amyloid plaques in Alzheimer's disease (AD).
https://www.stressmarq.com/wp-content/uploads/Amyloid-plaque_formation.jpg

BRAIN ATROPHY :- Loss of brain tissue and the death of nerve cells are the hallmarks of cerebral atrophy. A notable decrease in brain volume has been connected to the progressive cognitive deterioration associated with Alzheimer's disease. Specifically, the hippocampal tissue is the first region of the brain to atrophy, which causes cognitive decline and eventually memory loss.[42]

STRESS VIA OXIDATION :- Reactive oxygen species (ROS) are produced in excess during oxidative stress, which results in oxidative damage to cells and organs. Oxidative stress is brought on by an imbalance in the redox state. Prior research has demonstrated that AD patients exhibit substantial oxidative damage brought on by aberrant tau neurofibrillary tangle development and amyloid beta accumulation. [43]

❖ **METHOD:-**

1) Oxidative stress is brought on by an increase in reactive oxygen species (ROS) Production.
2) Neural death is a result of both mitochondrial malfunction and oxidative damage to neurons.[44]

CHOLINERGIC HYPOTHESIS:- Significant decrease in acetylcholine levels as a result of cholinergic neuron death. Reduced acetylcholine levels have been linked to memory loss and cognitive impairments Citation. [45]

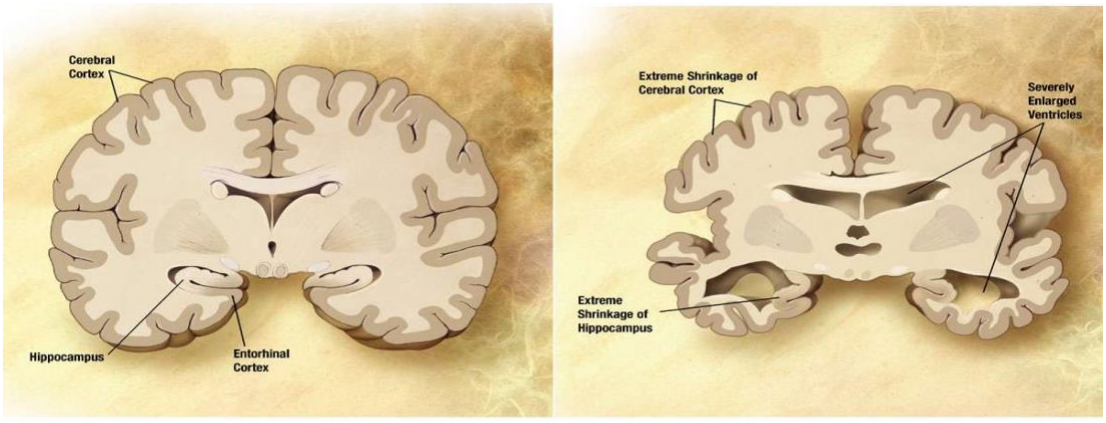
NEUROINFLAMMATION :- Chronic inflammation of the central nervous system, or "neuroinflammation," is linked to neurodegenerative illnesses and causes aberrant brain activity. Microglia are triggered in cases of neuroinflammation as an immunological reaction to amyloid beta plaques.[46]

METHOD:

1) Tau tangles and Aβ plaques cause astrocytes and microglia to become chronically activated.
2) Neuroinflammation plays a role in the development of neuronal injury and illness.[47]

MECHANIUM OF SYNAPTIC DYSFUNCTION

1) Tau tangles and Aβ oligomers disrupt synaptic transmission.
2) Deficits in synaptic transmission result in memory loss and compromised cognitive abilities.
3) In AD, there is a strong correlation between the degree of cognitive decline and synaptic loss.[48]



A representation of the normal human brain on the left, and the brain affected by Alzheimer's disease on the right.

https://www.best-alzheimers-products.com/alzheimers-disease.html

MECHANISMS OF ACTION OF CURCUMIN IN ALZHEIMER'S DISEASE

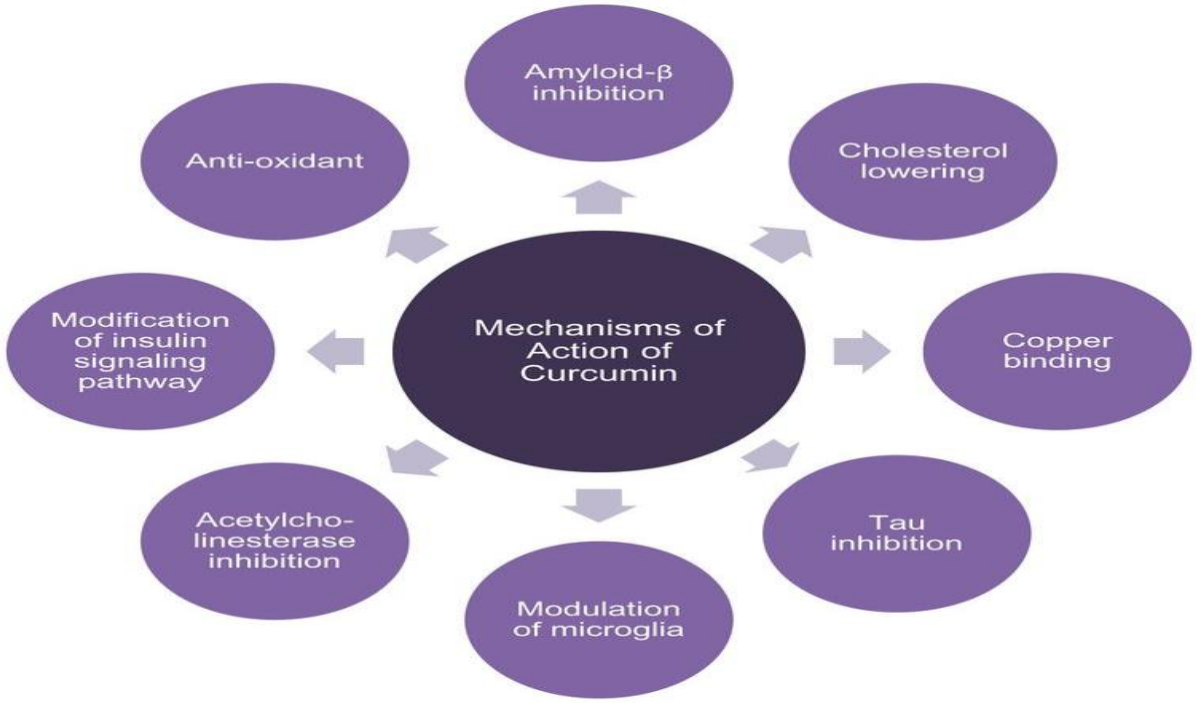
Pleiotropic methods of action are exhibited by curcumin. It specifically targets tau and A, the two histology hallmarks of AD. Curcumin also affects other facets of the illness process. In addition, it is an antioxidant, binds collagen, decreases cholesterol, alters microglial activity, blocks acetylcholinesterase, and strengthens the insulin signalling system.

AB INHIBITION :-

Since the characteristic hallmark of AD is the deposition of A plaques, curcumin has been investigated for its potential to stop A from forming and accumulating. Administering intragastric curcumin to a mouse model of AD decreased the production of A by suppressing the expression of BACE1, the enzyme responsible for cleaving APP into A. The rats given curcumin showed better memory and spatial learning outcomes, as well as relief from synaptic degeneration [49]. Likewise, Di Martino and associates [50] found curcumin to be an in vitro BACE1 inhibitor.[50]Presenilin-1 (PS-1), a glycogen synthase kinase-3 (GSK-3) substrate and a protein in the ~-secretase complex, is another enzymatic target for the synthesis of A. Between {-secretase and GSK-3} each involved in the production of A}. Curcumin treatment significantly decreased the amount of A produced by human neuroblastoma SHSY5Y cells. Additionally, there was a dose- and time-dependent drop in the levels of PS-1 and GSK-3} protein, indicating that curcumin reduced the generation of A} via inhibiting GSK-3}-dependent PS1 activation.[51]

Apart from preventing the synthesis of A, curcumin has also been shown to prevent fibrillar A from aggregating and to promote its disintegration both in vitro and in vivo.[52][53] In artificial lipid bilayers, curcumin inhibited A-membrane interactions and decreased A-induced membrane rupture, potentially avoiding significant calcium influx and cell death [54].

.. Through its role in regulating the phosphorylation of the NMDA receptor produced by Aβ, curcumin may also inhibit the rise of intracellular calcium . Curcumin may also change the A aggregation route so that harmless conformers develop instead of causing harm. Thapa and associates.[55] .



https://content.iospress.com/articles/journal-of-alzheimers-disease/jad170188

many pathways of action by which curcumin provides neuroprotection in AD are depicted in this flowchart. The substance prevents the synthesis of amyloid- and hyperphosphorylated tau, two histology hallmarks of AD, from occurring as well as their neurotoxicity. Curcumin also affects other facets of the illness process. It is an antioxidant, binds copper, decreases cholesterol, alters microglial activity, prevents acetylcholinesterase, and improves the insulin-signalling system.[55]

CHOLINERGIC AUGMENTATION THERAPY

Choline and lecithin, which are precursors of acetylcholine, have no effect on Alzheimer's patients.[56] due to their inability to elevate central cholinergic activity. [57] Adverse consequences of postsynaptic cholinergic receptor agonists have been deemed undesirable.[58,59] The use of cholinesterase inhibitors, also known as anticholinesterases, has produced positive results because they enhance cholinergic synaptic transmission by blocking acetylcholinesterase in the synaptic cleft, which reduces the amount of acetylcholine that is released from presynaptic neurons by hydrolysis. The method that each medication in this class inhibits acetylcholinesterase activity varies. [62] Reversible inhibitors, like donepezil and tacrine, attach to acetylcholinesterase and prevent the formation of the acetylcholine-enzyme complex.[63] "Pseudo irreversible" inhibitors, like rivastigmine, directly lower enzyme activity

rather than preventing the formation of the enzyme-acetylcholine complex. These medications' duration of action is dependent on both the kind of inhibition generated and the rate at which enzyme resynthesis occurs. The selectivity of anticholinesterases varies depending on the kind of cholinesterase. While donepezil and rivastigmine are selective inhibitors of acetylcholinesterase, tacrine and physostigmine inhibit both butyrylcholinesterase and acetylcholinesterase.[61]

PHYSOSTIGMINE :- Tertiary amine physostigmine inhibits both butyryl and acetylcholinesterase nonselective and reversibly. Because of the 30-minute plasma half-life of physostigmine, it was necessary to administer the drug every two hours during the initial trials.[64,65] A controlled-release formulation administered twice daily reduced scores on the cognitive subscale of the Alzheimer's Disease Assessment Scale by 2.4 percent 1111 in a six-week multicenter trial with patients (as previously described).[66] In both trials, the majority of patients did not finish the investigation.[66,67]

TACRINE

Tetrahydroaminoacridine, often known as tacrine, is a nonselective, reversible anticholinesterase that was given the go-ahead to treat Alzheimer's in 1993. Given its two to four hour plasma half-life, it needs to be administered four times a day. As food intake increases, absorption falls. Tacrine has been the subject of several quick studies.[68]

Those randomly randomized to receive 160 mg of tacrine daily in a 30-week study of 663 patients saw a 5.9 percent decrease in their score on the cognitive subscale of the Alzheimer's Disease Assessment Scale.[69] Less people (3%) and (4%), respectively, died or went into nursing homes among those who were able to continue taking tacrine than among those who took lower dosages (7% for both).Because tacrine produces asymptomatic elevations in serum aminotransferase concentrations, its use has been restricted.[68,70]

THE EPTASTIGMINE :-

Eptastigmine is a reversible inhibitor of anticholinesterase and a carbamate derivative of physostigmine.24 Over 700 patients were randomized at random to receive either a low dose of eptastigmine (45 mg daily) or a high dose (60 mg daily) of the medication or a placebo in two 24-week trials.[71,72] Patients administered 45 mg or 60 mg of eptastigmine experienced a 3 percent drop in the Alzheimer's Disease Assessment Scale cognitive subscale score and a 5 percent reduction in the Clinician Interview-Based Impression of Change scale score.[71] 0 have led to the clinical trial's continued suspension.[69]

TREATMENT OF THE BEHAVIORAL MANIFESTATIONS OF ALZHEIMER'S

DEPRESSION:-

Five to eight percent of patients with Alzheimer's disease experience major depression.[73,74] Approximately 25% of individuals experience depression at the outset of memory loss.[75] Despite their widespread use, there aren't many published studies on the use of antidepressants in Alzheimer's patients.[76] In 61 Alzheimer's patients, imipramine, a tricyclic anti epressant, had equivalent effects to a placebo in terms of reducing depression .[77] In a crossover trial including 26 depressed Alzheimer's patients, clomipramine and a placebo were administered for six weeks each. The outcome of both treatments was a 40–50% decrease in the Hamilton Depression Rating Scale score.[78,79]

The Mini-Mental State Examination score decreased as a result. In addition, 91 percent of patients experienced dry mouth, 64 percent experienced dizziness, and 45 percent experienced sleep disturbance. When compared to a placebo, the serotonin-reuptake inhibitor citalopram improved the patient's depression rating score by 20%. A depression rating scale score improved by 20% more with citalopram, a serotonin-reuptake inhibitor, than with a placebo.[80]

SLEEP DISTURBANCES :-

The phases of rapid eye movement and non-rapid eye movement sleep steadily decrease as Alzheimer's disease progresses, but the proportion of time spent awake rises.[81]

"Sundowning" is a term used to describe delirium that manifests in the evening or at night and either goes away or gets better during the day is linked to sleep disturbance. Alzheimer's disease patients experience sleep problems in 30% of institutionalized patients and 10% of ambulatory patients; these sleep disturbances may be related to brain stem degeneration.[82][83]

Adverse effects can result from a variety of treatments, including sedatives and neuroleptic medications. Reducing naps during the day, limiting the amount of time spent in bed, and exposing oneself to bright light when awake may also be beneficial, however these measures have not been thoroughly studied.[81]]

PREVENTION :- The number of senior people at risk for Alzheimer's disease is likely to rise, and the associated costs have prompted the investigation of preventive treatments. The development of safe therapies or interventions that might be applied to a large number of older people at risk—many of whom might never develop the disorder—will be necessary to prevent Alzheimer's disease.[84,85] Potential preventive treatments being considered are amyloid production-directed vaccines, oestrogen-replacement therapy [84,85] nonsteroidal anti-inflammatory medications , and other continuing lines of inquiry.[85]

WANDERING :-

Any stage of Alzheimer's disease can result in wandering from home or a medical facility, and the frequency of these incidents rises with a decline in cognitive ability and independence in daily tasks. A community-based study discovered that 36% of Alzheimer's patients wandered.[86] physical environment by concealing doorways and encouraging movement under supervision may limit wandering.[87]

ALZHEIMER'S DISEASE BENEFITS: -

There are certain unintended benefits connected to research, awareness, and society responses, even though it is difficult to pinpoint actual "advantages" of a condition as terrible as Alzheimer's:

i. Enhanced Research and Awareness: The incidence of Alzheimer's disease has prompted substantial financing for research and scientific investigation, resulting in advancements in the fields of neurobiology, genetics, and possible treatment strategies.[89]

ii. Better Care and Support Systems: As a result of caregiver support programs, higher standards of care, and enhanced patient quality of life assessments, Alzheimer's patients are now better supported.[90]

iii. Public Knowledge and Education: As a result of greater public knowledge and education on dementia, stigma is lessened and early diagnosis and intervention are encouraged.[92]

iv. Developments in Related Therapies: Studies on Alzheimer's have sparked improvements in neurodegenerative illnesses, cognitive decline, and aging processes, among other related fields of medicine.[88]

v. Increased Community Support Networks and Stronger Family and Community Bonds: In certain situations, communities and families unite more closely to assist those suffering from Alzheimer's disease, resulting in enhanced social networks and community support systems.[91]

ADVERSE EFFECTS OF ALZHEIMER'S DISEASE :-

Cognitive Decline: The biggest drawback is the steady deterioration of cognitive function, which causes memory loss, faulty reasoning, and issues with language and spatial awareness. Both everyday functioning and quality of life are negatively impacted by this deterioration.

- Impact on Emotions and Psychosis: Patients and their families frequently go through a lot of emotional and psychological strain. Patients experience a progressive loss of identity and independence, while caretakers bear a significant emotional strain.[93]

- Economic Burden: The expenses of care, drugs, and lost productivity associated with Alzheimer's disease place a heavy financial strain on families and healthcare systems.[94]

- Loss of Autonomy: As the illness worsens, people become less able to handle personal matters and carry out everyday tasks on their own, necessitating round-the-clock care and monitoring.[95]

- Increased Risk of Physical Health Problems: Individuals with AD are more susceptible to infections and consequences resulting from immobility.

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