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RESEARCH ARTICLE

ALZHEIMERS DISEASE: FROM CLINICAL PRESENTATION TO THERAPEUTIC STRATEGIES

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Abstract

Alzheimers disease (AD) is the most common form of dementia, primarily affecting individuals over the age of 65. It is a progressive neurodegenerative disorder that impairs memory, cognition, language, and decision-making abilities. AD progresses through stages—from a preclinical phase with no visible symptoms, to mild cognitive impairment, and eventually to dementia, which ranges from mild to severe. Although AD does not directly cause death, it increases the risk of life-threatening complications. The underlying mechanisms of AD are complex and multifactorial, involving both genetic and environmental factors. Familial AD results from specific genetic mutations and appears early, while sporadic AD, the more common form, develops later in life and has unclear causes. Key pathological features include the buildup of amyloid-beta plaques and tau tangles, neuroinflammation, and widespread neuronal damage. Recent advances in biomarkers—such as PET imaging and fluid-based tests—have improved early detection and diagnosis. While no cure exists, emerging therapies aim to manage symptoms and slow disease progression. The complexity of AD pathogenesis continues to challenge the development of effective treatments, highlighting the need for a multifaceted approach to research and care.

Introduction:-

Dementia is a general term for a decline in thinking and memory skills that affects daily life. **Alzheimer's disease (AD)** is the most common type of dementia, especially in people over 65. It is a brain disease that develops slowly and worsens over time, affecting memory, understanding, language, attention, and decision-making.AD doesn't directly cause death, but it increases the risk of other serious health problems. The disease progresses in stages:

- **Preclinical stage** – no symptoms yet, but changes in the brain have begun.
- **Mild cognitive impairment (MCI)** – mild memory problems that don't yet affect daily life.
- **Dementia stage** – noticeable memory loss and other symptoms that interfere with daily activities. This stage is further divided into:
  - Mild

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- Moderate
- Severe

The first sign is often trouble remembering recent events, while long-term memories may remain intact. As the disease progresses, people may struggle with problem-solving, planning, language, and recognizing places or faces. Later, they may show mood changes, confusion, agitation, or even hallucinations. In the most severe stage, people lose the ability to walk, talk, control their bladder, and need full-time care.Over the past decade, researchers have developed biomarkers that help detect AD early. These include brain scans (PET imaging) and tests of spinal fluid or blood that look for signs of amyloid and tau proteins.There is no cure for Alzheimer's, but some treatments can help manage symptoms or slow the disease's progression. New drug discoveries and biomarkers have led to better ways of diagnosing and treating AD earlier than before[1].

Mechanism Of Alzheimer's Disease

- Alzheimer's disease (AD) is a complex brain disorder with no single clear cause. It comes in two main forms: familial AD (rare, caused by specific genetic mutations and starting earlier in life) and sporadic AD (more common, usually starting after age 65 and influenced by genes, environment, and lifestyle). Many genes have been linked to the common form, but the exact causes are still unclear. Other risk factors like poor health, stress, and environmental exposure may also play a role by affecting the body and brain in different ways. AD shows up in various ways—like memory loss, brain inflammation, and damage to brain cells—and symptoms can differ from person to person. Because of this complexity, it's hard to create a single theory that explains everything, and many treatments tested in clinical trials haven't worked, possibly because multiple disease mechanisms are happening at the same time[2].

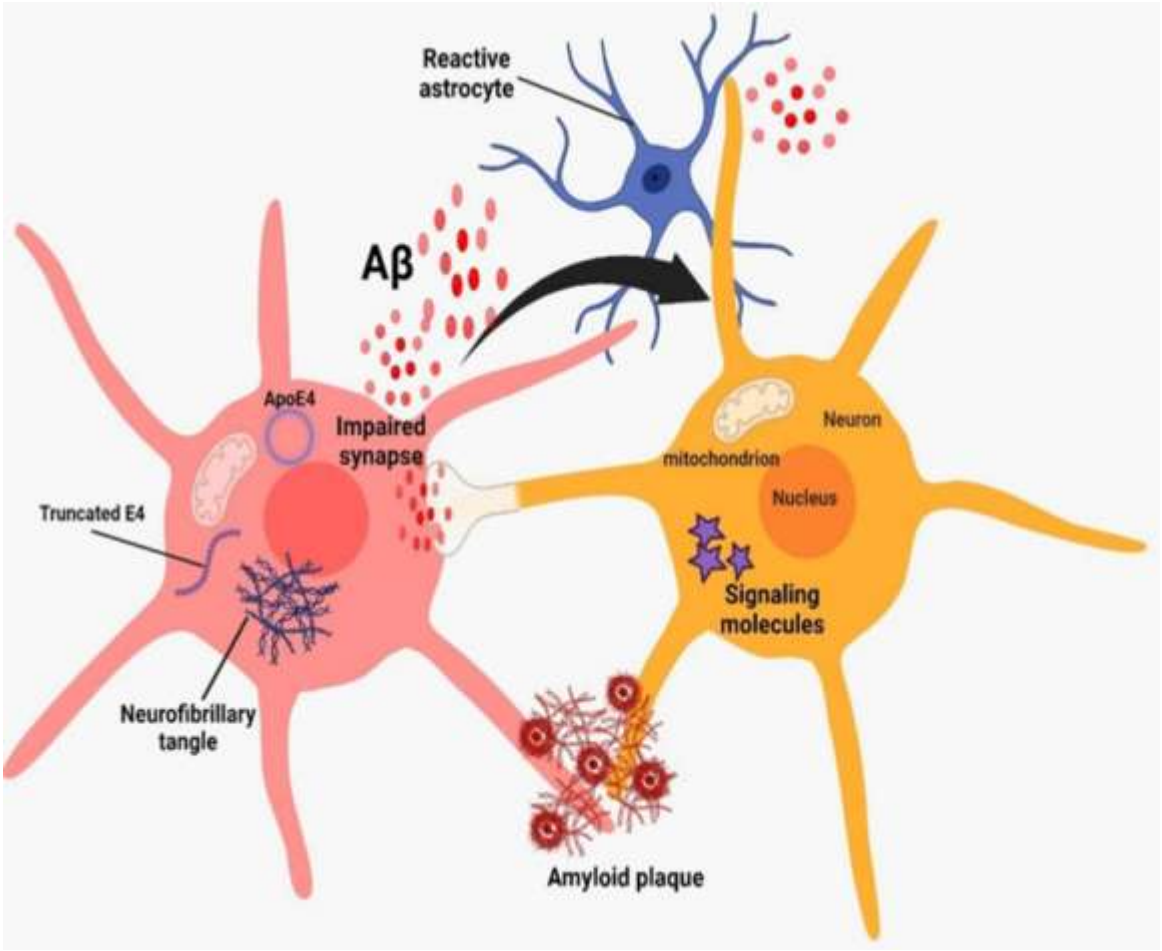


Figure1:- Alzheimer's pathogenesis based on two classical hallmarks on amyloid beta and neurofibrillary tangles[3]

There are different biological theories that explain what causes Alzheimer's disease. These include[2]:

1. **Cholinergic hypothesis** – Suggests that Alzheimer's involves reduced activity of acetylcholine, a brain chemical important for memory.
2. **Glutamate excitetoxicity hypothesis** – Too much glutamate overstimulates nerve cells, causing damage.
3. **Amyloid hypothesis** – Abnormal formation of beta-amyloid protein forms plaques in the brain, which harms brain cells.
4. **Tau protein hypothesis** – Tau proteins inside neurons become abnormally tangled, disrupting cell function.
5. **Inflammatory hypothesis** – The brain's immune cells (like microglia) get overactive, causing inflammation that damages neurons.
6. **Micro biota-gut-brain axis hypothesis** – Changes in gut bacteria affect the brain, possibly through inflammation and harmful microbial products.
7. **Abnormal autophagy hypothesis** – The cell's waste disposal system fails, leading to formation of damaged proteins and organelles.
8. **Metal ion hypothesis** – Too much metal (like iron or copper) causes harmful reactions in the brain, increasing oxidative stress[2].

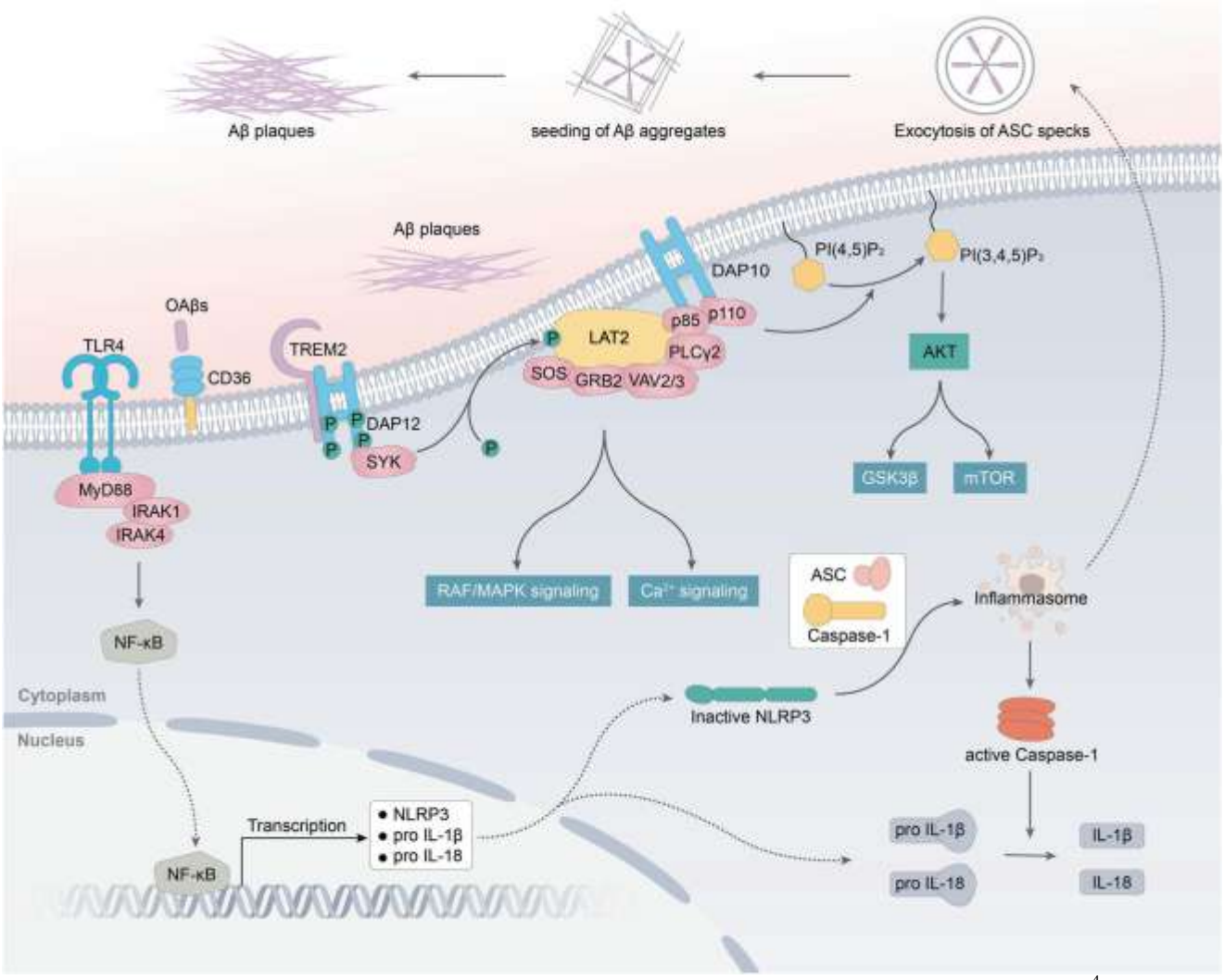


Figure2:- Schematic illustration depicting potential molecular downstream pathways of Aβ on microglia[4].

This diagram shows how amyloid-beta (Aβ) plaques, which build up in the brain in Alzheimer's disease, activate the brain's immune system and cause inflammation. Immune cells in the brain recognize Aβ through special receptors like TLR4**,** CD36, and TREM2. These receptors send signals that activate proteins like NF-κB, which then moves into the cell's nucleus and switches on genes that make inflammatory molecules such **as** IL-1β and IL-18**.** At the same time, other signaling pathways involving AKT**,** mTOR, and MAPK help activate a structure called the

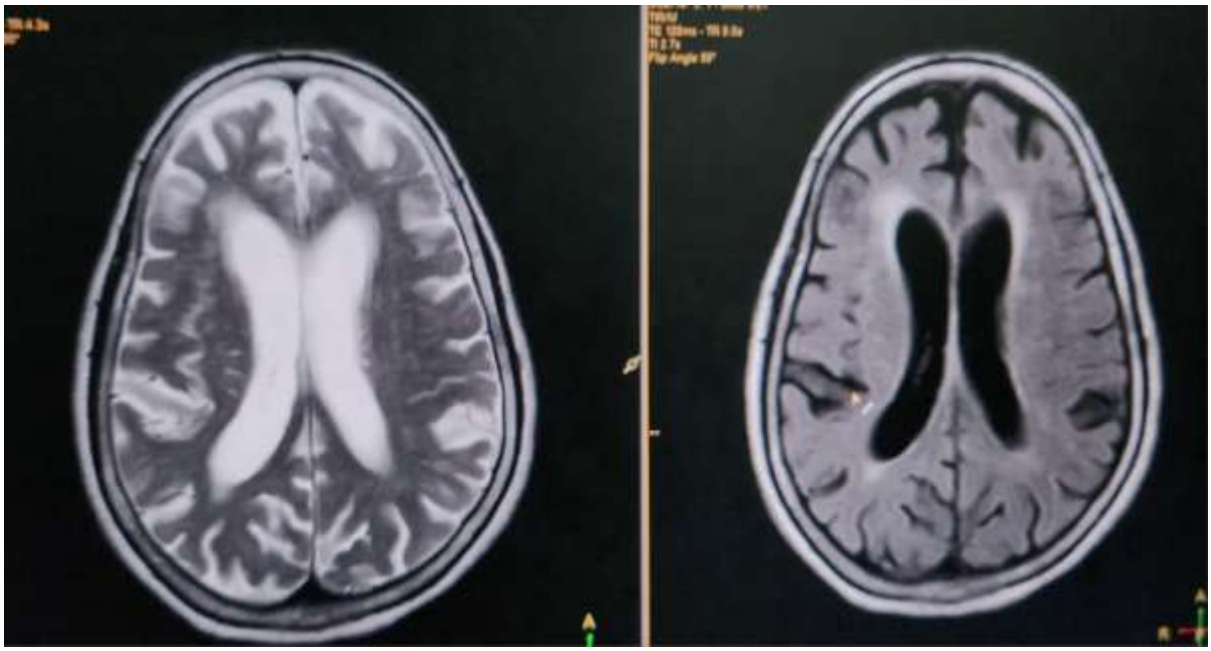
inflammasome**.** This structure turns inactive proteins into active ones like Caspase-1, which then activates IL-1β and IL-18, triggering inflammation. The process can repeat itself as inflammasome particles called ASC specks are released and help form more Aβ plaques, continuing the cycle of damage[4].

Clinical History Of Alzheimer's Disease

Patient		Name**:**Charju		Devi
Age/Sex:	70	years	/	Female

Date of MRI: 24/04/2025

The patient is a 70-year-old female with a history of progressive memory loss, difficulty in performing daily activities, and impaired orientation over the past few months to years. The clinical symptoms are suggestive of cognitive decline, raising suspicion forneurodegenerative disorder such as Alzheimer's disease. MRI Brain was advised for further evaluation at DR.RPGMC KANGRA at Tanda.



MRI shows Axial T2 and FLAIR Image showing diffuse cerebral atrophy with associated volume loss of gyri and widened sulci.

Here's the MRI report
Patient Name:
CHARJU DEVI **Age/Sex:**70Y / FEMALE **Date:** 24/04/2025

MRI Brain (PLAIN + CONTRAST)
(Sequences: Axial T1, T2, FLAIR, AXDWI, ADC, ANGRE, SAGT2, COR T2)
Findings:

- There is moderate diffuse cerebral atrophy with associated volume loss of gyri and widened sulci.
- Bilateral hippocampal atrophy is noted.
- Global Cortical Atrophy (GCA) score: 2, indicating moderate generalized atrophy.
- Medial Temporal Lobe Atrophy (MTA) score: 4, indicating severe hippocampal and peri hippocampal atrophy.
- Mild ex vacuo dilatation of the lateral ventricles is seen.
- Tiny WM spaces seen in the bilateral periventricular region
- Corpus callosum is normal.
- Sylvian fissures, insula, and basal ganglia are visualized normally.
- Bilateral CP angles clear. No mass lesion seen.

- Sellar, para-sellar, and suprasellar areas are normal.
- Major intracranial vessels show normal luminal caliber and flow void.
- Brainstem, cerebellum, and cervico-medullary junction appear normal.
- Scalp and calvaria normal.

Impression:
- Moderate cerebral atrophy (GCA 2) with prominent gyri volume loss.
- Severe medial temporal lobe atrophy (MTA 4) with ex vacuo dilatation of ventricular system.

Advice: Clinical correlation is recommended.

Imaging And Biochemical Markers of AD[5]

Among the neuroimaging techniques, FDG-PET serves as a functional biomarker that reveals early metabolic changes in the brain, especially in regions like the hippocampus. This can aid in the differential diagnosis of AD. Amyloid PET, on the other hand, provides direct visualization of Aβ deposition, a hallmark of AD pathology. While it offers specificity in distinguishing AD from other neurodegenerative diseases, its broader use is limited due to the presence of amyloid in some cognitively normal elderly individuals.

Biochemical markers in cerebrospinal fluid (CSF) are also useful for detecting early AD pathology. Key CSF biomarkers include reduced Aβ42 and elevated levels of phosphorylated tau (p-tau) and total tau (t-tau), reflecting amyloid plaque formation and tau pathology, respectively. CSF biomarker ratios, such as Aβ42/40, enhance diagnostic accuracy. However, while CSF analysis aids early detection, it does not indicate disease severity.

Functional brain imaging techniques such as Positron Emission Tomography (PET), functional MRI (fMRI), and Single-Photon Emission Computed Tomography (SPECT) are becoming increasingly valuable in mapping patterns of dysfunction in smaller brain areas of the medial temporal and parietal lobes. While these functional brain imaging techniques hold promise for early detection and monitoring of the clinical progression of AD, their role in the definitive diagnosis of AD is not fully established yet.

Pharmacological Approach(Fda-Approved Drugs)[3]

Symptomatic Treatments (pre-2021):

1. Cholinesterase Inhibitors (ChEIs) – For mild stages:
   - Tacrine (withdrawn due to liver toxicity)
   - Donepezil, Rivastigmine, Galantamine – Boost acetylcholine levels to improve symptoms.
   - These drugs have limited efficacy and mostly manage symptoms.
2. Memantine – For moderate-to-severe stages:
   - NMDA receptor antagonist, modulates glutamate to prevent neuronal damage.
   - Modest benefit, but with possible side effects like dizziness and hallucinations.

Disease-Modifying Treatments (from 2021 onward):

1. Aducanumab (Aduhelm™) – Approved June 2021 (Stages 3–4):
   - Targets amyloid-beta (Aβ) protofibrils.
   - Controversial due to safety issues (brain swelling, bleeding) and uncertain benefits.
2. Lecanemab (Leqembi™) – Accelerated approval in Jan 2023, full approval in July 2023:
   - Also targets Aβ protofibrils, with clearer evidence of slowing memory loss.
   - Associated with amyloid-related imaging abnormalities (ARIA).
3. Donanemab – Approved on July 2, 2024 based on TRAILBLAZER-ALZ 2 (Phase 3 trial):
   - Monthly IV infusion (350 mg/20 mL).
   - Another anti-Aβ monoclonal antibody, similar in mechanism and side effects to lecanemab and aducanumab.
   - Shows potential but still carries risks like ARIA and brain shrinkage.

Table I:- Cholinesterase Inhibitors[6]

Drug name	Dosage
DONEPEZIL	5-10 mg PO qhs
GALANTAMINE	8-12 mg PO bid
RIVASTIGMINE	2-6 mg PO bid

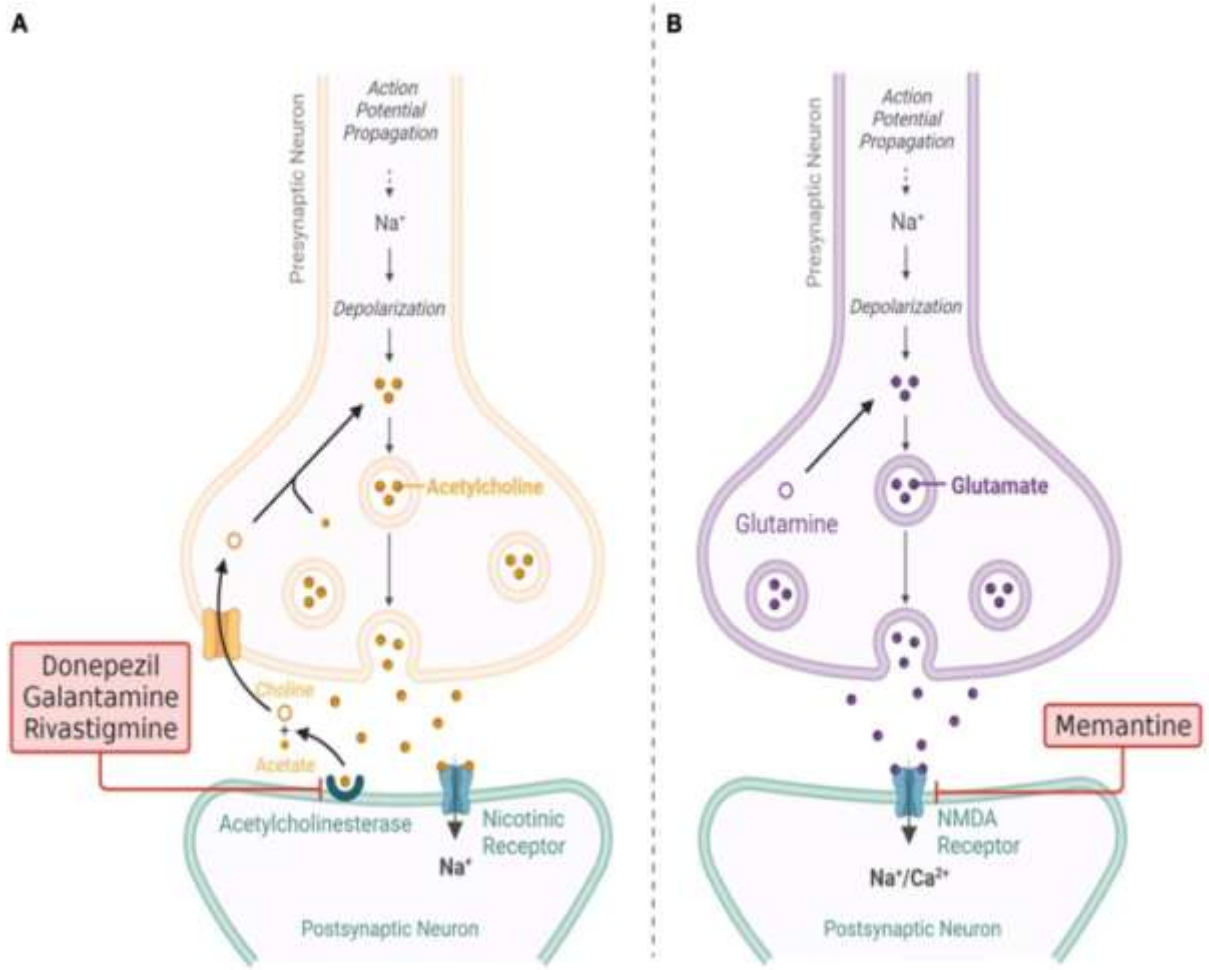


Figure3:- (A) Visualization of current drugs (donepezil, galantamine, rivastigmine). (B) mechanism of action of memantine for Alzheimer's disease (AD)[3].

Emerging Treatments[3]

Microbiota-Gut-Brain Axis & Astrocytes in Alzheimer's Disease

Recent studies show that gut bacteria can influence brain cells, especially astrocytes, which are key for brain health. In Alzheimer's Disease (AD), changes in gut microbiota seem to reduce harmful inflammation in the brain, helping astrocytes stay balanced. Interestingly, these protective effects are stronger in male mice. However, when the gut microbiota is restored or when short-chain fatty acids (SCFAs) are added, these benefits decrease. This suggests a complex link between gut health and brain disease, and that sex differences may matter.

40 Hz Brain Rhythm Stimulation in Alzheimer's Disease

Stimulating the brain at 40 Hz (gamma frequency) using touch (vibration), light, or sound may help reduce Alzheimer's symptoms. A recent study showed that tactile stimulation (vibrating the cage of mice at 40 Hz) improved brain activity, preserved brain cells, reduced tau proteins, and enhanced motor skills in Alzheimer's mouse models. This method, called GENUS (Gamma Entrainment Using Sensory stimuli), might protect neurons and improve brain function in early AD.

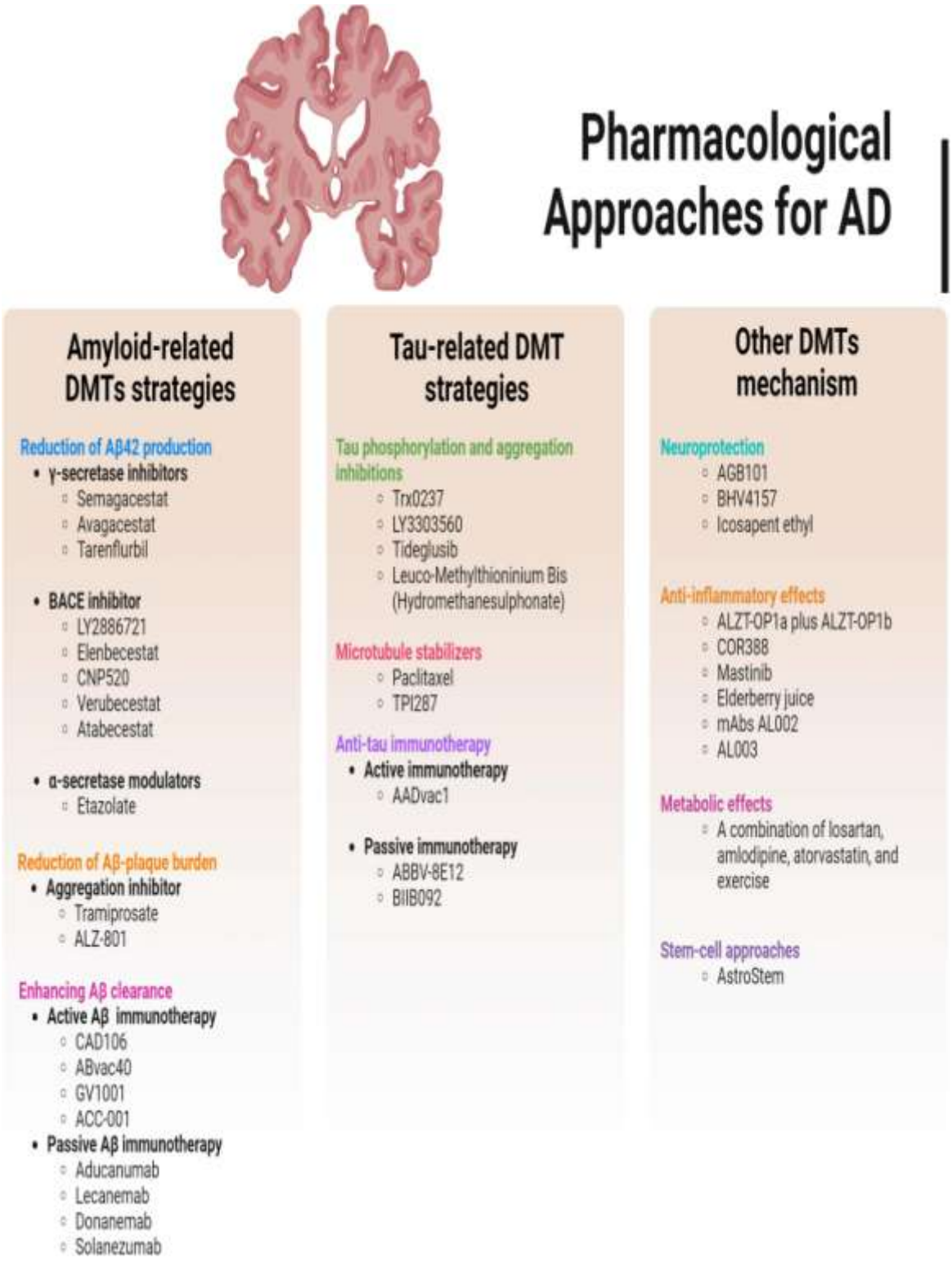


Figure 5:-Pharmacological Approaches For Alzheimer Disease[3]

Non-Pharmacological Approaches To Dementia[3]

Cognitive Training

People with early Alzheimer's disease (AD) or vascular dementia often struggle with memory. Cognitive training and rehabilitation are non-drug methods that aim to improve thinking skills and help with daily tasks.

These methods focus on improving brain functions like memory, reasoning, and how quickly information is processed. Activities can be simple, like using the non-dominant hand, which helps stimulate the brain at no cost. Learning new things—such as a new language—or playing games like cards or board games can also help. These activities not only challenge the brain but also support social connections, which is important for mental well-being.

Some research shows that cognitive training can help slow memory decline, especially in mild to moderate Alzheimer's. However, more large-scale, long-term studies are needed to confirm this. Since cognitive training doesn't have side effects, it's a good option when medications aren't suitable.

Physical Exercise, Ergo therapy, and Brain Stimulation

Exercise is good for everyone, including people with Alzheimer's. Research shows that regular moderate exercise, like walking or swimming, can improve memory and brain function. It may even help grow the hippocampus, a part of the brain involved in memory.

Though results vary, exercise is still considered beneficial. It may work by improving blood flow to the brain.

Ergotherapy, or occupational therapy, helps people with dementia improve their daily life skills and maintain independence. It can also increase quality of life and happiness.

Physical activity also helps with emotional issues like anxiety and depression. It can reduce the need for medications and improve mood and behavior. Plus, it encourages social interaction, which helps people stay connected and feel more independent.

Combined Approaches

Drugs like cholinesterase inhibitors and memantine help with symptoms but don't stop the disease. Combining medications with non-drug methods like cognitive training and exercise may offer better results for both patients and caregivers[3].

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