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APOPTOSIS UNVRAVELED: THE NEURONAL PRESPECTIVE

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ABSTRACT:
Alzheimer's disease is a progressive neurodegenerative disorder characterized by cognitive decline, memory impairment, wide spread neuronal loss, particularly in the hippocampus and cerebral cortex. A central mechanism contributing to neuronal degeneration in Alzheimer's disease is apoptosis, a genetically regulated and energy dependent form of programmed cell death. In this diseased brain, excessive activation of apoptotic pathways results from multiple pathological factors, including amyloid beta accumulation, tau hyperphosphorylation, mitochondrial dysfunction, oxidative stress, calcium dysregulation and chronic neuroinflammation. Apoptosis in Alzheimer's disease primarily occurs through the intrinsic (mitochondrial) and extrinsic (death receptors) pathways. The intrinsic pathway is triggered by mitochondrial damage, leading to cytochrome-c release, apoptosome formation, activation of caspase -9 and caspase-3. The extrinsic pathway is mediated by inflammatory cytokines such as TNF-α and Fas ligand which activate caspase-8 and subsequently caspase-3. Both pathways converge on executioner caspase, resulting in DNA fragmentation, protein degradation and control neuronal death. Key molecular regulators include Bcl-2 family proteins, caspases, p53, apaf-1, reactive oxygen species and calcium signaling mechanism. The imbalance between pro- apoptotic and anti- apoptotic factors favors neuronal loss, contributing to brain atrophy and progressive cognitive dysfunction. Current therapeutic approaches, including cholinesterase inhibitors, NMDA receptors antagonist and monoclonal antibodies targeting amyloid plaques, provide symptomatic relief but do not fully prevent neuronal apoptosis. Therefore, understanding apoptotic mechanisms offers significant potential for developing targeted therapies aimed at reducing neurodegeneration and slowing disease progression in Alzheimer's disease.

Abbreviation:
Aβ(Amyloid-Beta), Apaf-1(Apoptotic Protease Activating Factor-1), ATP (Adenosine Triphosphate), Bcl-2(B cell Lymphoma-2), Bcl-Xl (B cell Lymphoma-Extra Large) , DISC (Death Inducing Singling Complex), DNA (Deoxy Ribose Nucleic Acid), FDA (Food and Drug Administration), NMDA (N-Methyl-D-Aspartate), PCD (Programmed Cell Death, ROS(Reactive Oxygen Species), TNF-α (Tumor Necrosis Factor -Alpha).

1. INTRODUCTION:

Apoptosis is a genetically regulated form of programmed cell death (PCD) that enables organisms to eliminate unwanted, damaged, or potentially harmful cells in a controlled and energy – dependent manner. In the nervous system, apoptosis plays a fundamental role in both development and homeostasis. During neural development, neurons are generated in excess and a significant proportion are selectively eliminated through apoptosis to ensure proper matching between neurons and their target cells, thereby refining neural circuits. This process is tightly regulated by neurotrophic factors, intracellular signaling pathways, and gene expression programs (Oppenheim 1991 & Yuan & Yankner,2000). In the mature nervous system, neuronal apoptosis is less frequent but remains biologically important. It can be triggered by cellular stressors such as DNA damage, oxidative stress, mitochondrial dysfunction, and excitotoxicity. Dysregulation of apoptotic pathways has been strongly implicated in the pathogenesis of several neurological disorders, including Alzheimer's disease, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis (Mattson, M.P. 2000 & Friedlander, R.M. 2003). Because neurons are largely post-mitotic and irreplaceable, precise control of apoptotic mechanisms is critical for maintaining nervous system integrity. At the molecular level, neuronal apoptosis is primarily mediated through intrinsic (mitochondrial) and extrinsic (death receptor) pathways that converge on the activation of caspases, a family of cysteine proteases responsible for the characteristic biochemical and morphological features of apoptosis. Apoptosis is a form of programmed cell death that allows organisms to remove unnecessary, damaged, or potentially harmful cells in a controlled manner. In the nervous system, apoptosis is crucial both during development and in disease. A recent study showed that silibinin, a bioactive compound, can significantly reduce neuronal apoptosis and synaptic dysfunction in Alzheimer's disease models by modulating signaling pathways that protect neurons from amyloid-β (Aβ)-induced death. It also decreased Aβ deposition and neuroinflammation, suggesting potential therapeutic value (Song, X., et al.2020). Newer studies are linking immune imbalance-including cytokines and chemokines to neuronal apoptosis and degeneration in Alzheimer's disease. Chronic neuroinflammation can prime apoptotic pathways, increasing neuronal vulnerability (Heneka, M. T., et al 2015 & Calsolaro, V., & Edison, P. 2016).

1.1. Importance of apoptosis in Alzheimer disease:

Neuron loss:

a) Alzheimer's is marked by progressive loss of neurons, especially in the hippocampus and cortex (areas for memory and thinking) (Braak, H., & Braak, E. 1991).
b) Apoptosis is one of the main mechanisms driving this neuron death (Yuan, J., & Yankner, B.A. 2000).

Amyloid -beta toxicity:

a) Disrupt calcium balance.
b) Damage mitochondria.
c) Generate oxidative stress.
d) These stresses activate apoptotic pathways-neurons undergo programmed death (Mattson 1992, Reddy & Beal 2008, Butterfield & Lauderback 2002, Kuo 1996).

Mitochondrial dysfunction:

a) Mitochondria regulate energy and apoptosis.
b) Reduces energy supply.
c) Release pro- apoptotic factors.
d) This promotes neuronal apoptosis (Lin, M. T. & Beal 2006, Kroemer & Reed 2000, Mattson, M.P. 2000).

Neuroinflammation:

a) Chronic inflammation in the brain (from activated microglia and astrocytes).
b) Release cytokines and toxic molecules.
c) These can activate apoptotic signaling in neurons (Akiyama 2000, Griffin 1998, Li, M., et al. 2003).

Therapeutic Target:

a) Modulating apoptosis could be potential strategy to slow neurodegeneration in Alzheimer's Disease.
b) Researchers are exploring ways to inhibit excessive apoptosis or promote neuronal survival (Cumming, J., et al. 2019, Huang, E.J., & Reichardt 2001).

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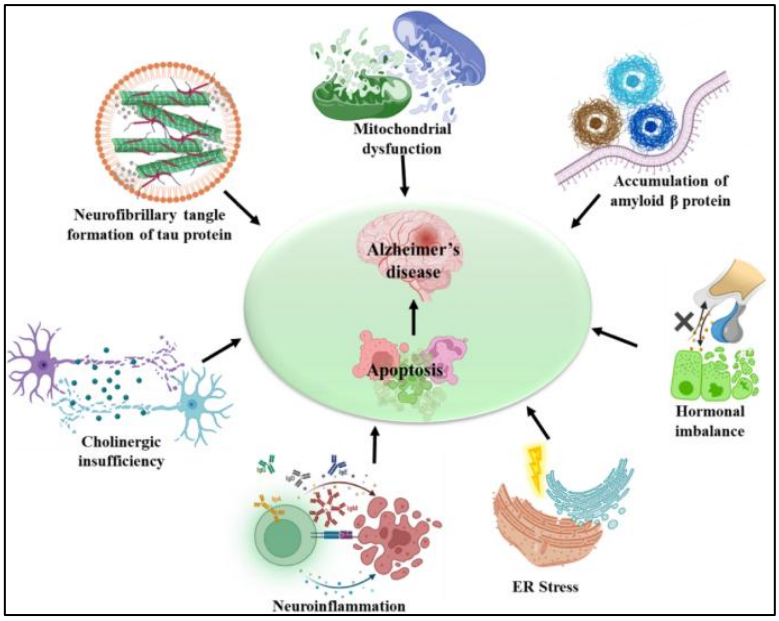

Figure:1

1.2 Mechanism of Apoptosis in Neurons (Alzheimer's Disease):

Apoptosis in Alzheimer's Disease occurs mainly through amyloid – beta toxicity, tau pathology, mitochondrial dysfunction, oxidative stress and neuroinflammation, which activate both the intrinsic (mitochondrial) and extrinsic (death receptor) apoptotic.

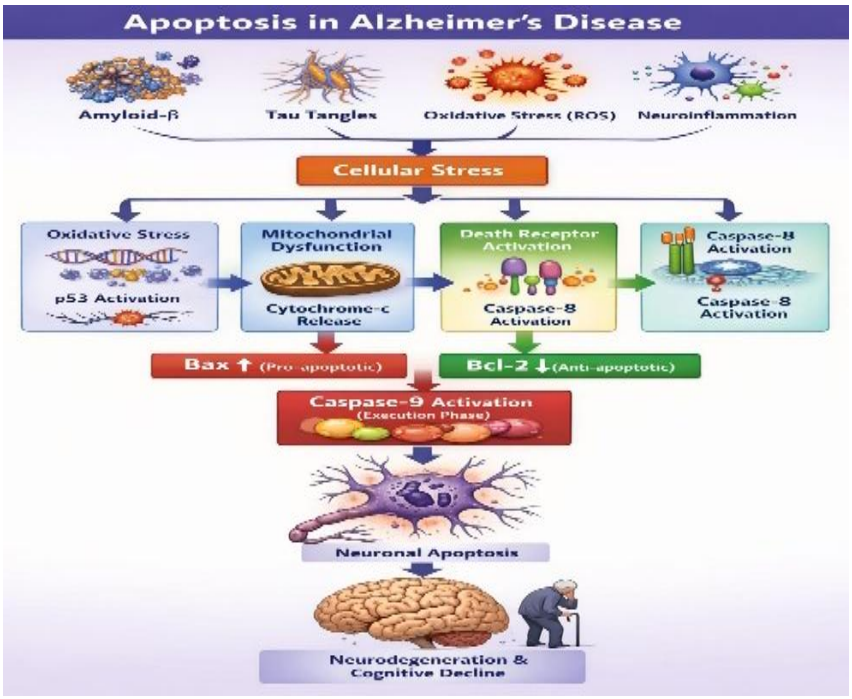

Figure: 2

1.2.1 Intrinsic (Mitochondrial) Pathway:

The intrinsic pathway is primarily triggered by internal cellular stress and is considered the dominant apoptotic mechanism in Alzheimer's disease. In Alzheimer's disease, amyloid-beta peptides and hyperphosphorylated tau proteins induce mitochondrial dysfunction. These abnormalities impair the electron transport chain, increase reactive oxygen species (ROS) production and reduce ATP synthesis.

Oxidative stress and calcium imbalance further damage mitochondria. This stress alters the balance of Bcl-2 family proteins, increasing pro-apoptotic proteins (Bax, Bak, Bad) and decreasing anti-apoptotic proteins.
As a result, mitochondrial outer membrane permeabilization occurs, leading to the release of cytochrome-c into the cytoplasm. Cytochrome-c binds with Apaf-1 and procaspase-9 to form the apoptosome, which activates caspase-9. Caspase-9 then activates caspase-3, the executioner caspase. Caspase-3 degrades cellular proteins, fragments DNA and leads to controlled neuronal death (Reddy & Beal 2008, Cesta, M.C., etal.2018).

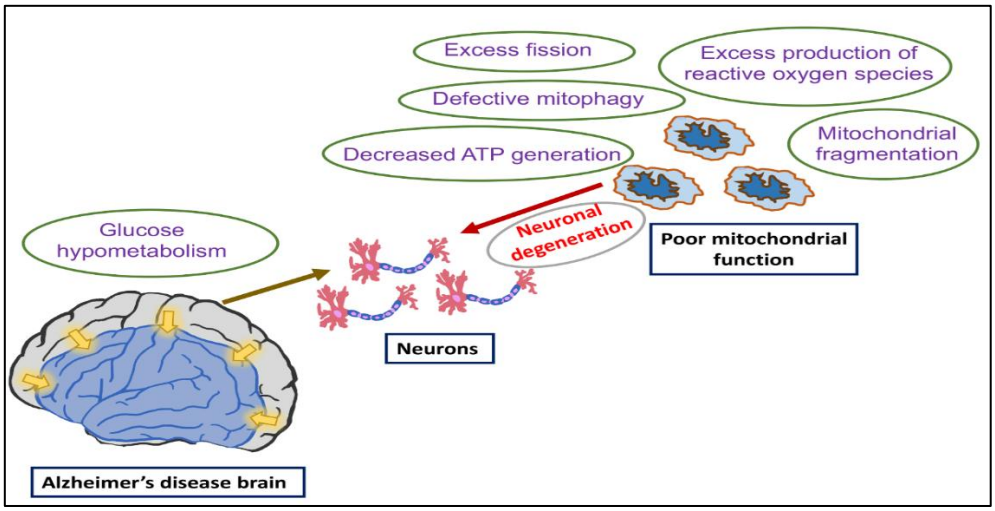

Figure:3

1.2.2 Extrinsic (Death Receptor) Pathway:

The extrinsic pathway is initiated by external signals, mainly inflammatory processes seen in Alzheimer's disease. Chronic neuroinflammation in Alzheimer's disease activates microglia and astrocytes, which release inflammatory cytokines such as TNF-α and Fas ligand.

These ligands bind to death receptors (TNF receptor and FAS receptor) on neuronal membranes. Ligand binding leads to formation of the death- inducing signaling complex (DISC), Which recruits adaptor protein like FADD. This complex activates caspase-8.

Activated caspase-8 can directly activate caspase-3, leading to apoptosis. It can also cleave Bid into truncated Bid, which interacts with mitochondria and promotes cytochrome-C release, thereby linking the extrinsic pathway to the intrinsic pathway (Haass, C., & Selkoe 2007, Zhang, Y., et al. 2018).

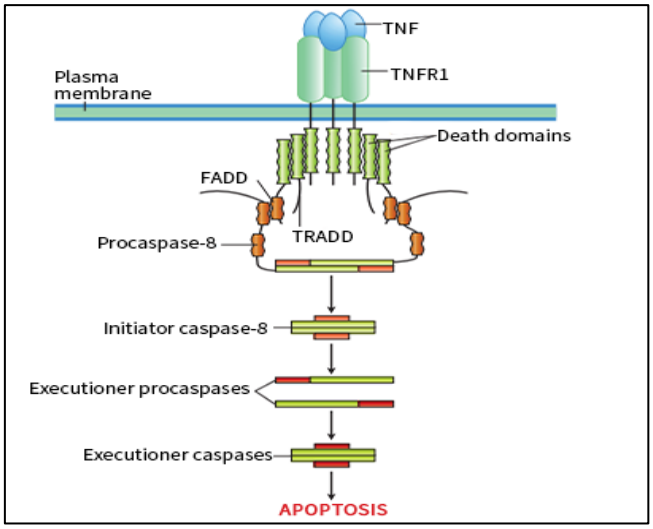

Figure:4

1.2.3 Pathway Interaction:

Both pathways converge on caspase-3 activation, which executes apoptosis. Cross- talk between pathways amplifies neuronal death in Alzheimer's Disease (Li, J., et al. 2018, Zhang. Y., et al. 2017).

2 Regulators Of Apoptosis in Neurons (Alzheimer's Disease):

Apoptosis in Alzheimer's disease is tightly controlled by several molecular regulators that either promote (pro-apoptotic) or inhibit (anti- apoptotic) neuronal death. In Alzheimer's Disease, imbalance between regulators favors neuronal loss (Mattson 2000, Friedlander, R.M. 2003).

2.1 Bcl-2 Family Proteins (Central Regulators):

The Bcl-2 family of proteins are the most important regulators of the intrinsic (mitochondrial) apoptotic pathway. They determine whether a neuron survives or undergoes apoptotic by controlling mitochondrial membrane permeability.

Anti-apoptotic members: -

a) Bcl-2
b) Bcl-Xl

These proteins stabilize the mitochondrial outer membrane and prevent the release of cytochrome-C. In healthy neurons, they support cell survival. In Alzheimer's disease, their expression is often reduced, making neurons more vulnerable to apoptosis (Youle & Strasser, A.2008).

2.2 Caspases (Execution Regulators):

Caspase are cysteine-aspartate proteases that execute apoptosis. They exist as inactive precursors and are activated during apoptotic signaling.

Types: -

Initiator caspases: caspase-8 (extrinsic pathway), caspase-9 (intrinsic pathway)
Executioner caspase: caspase-3, caspase-6, caspase-7
Role in Alzheimer's Disease: -

a) Caspase-3 is particularly important in Alzheimer's disease.
b) Cleaves structural and nuclear proteins
c) Causes DNA fragmentation
d) Leads to neuronal shrinkage and death
e) Elevated caspase-3 activity has been detected in Alzheimer's Disease brains, suggesting its major role in neurodegeneration (Riederer, P., et al. 2001).

2.3 P53 (Tumor suppressor protein):

P53 is a protein in our cells that helps controls cell death (Apoptosis), especially when a cell is damaged or stressed.

In Alzheimer's disease:

a) Harmful stress and DNA damage in brain cells turn on p53
b) P53 than tells the cell to make proteins (like Bax) that cause cells death
c) It also reduces proteins (like Bacl-2) that normally protect the cell from dying
d) Because of this, the balance shifts towards more cell death.
e) Scientist have found higher levels of p53 in brain cells that easily damaged in Alzheimer's disease (Culmsee & Mattson 2005).

2.4 Apaf-1 (Apoptotic protease activating factor-1):

Apaf-1 is a protein that helps start the process of cell death (Apoptosis)

a) In Alzheimer's disease a Mitochondria often do not work properly
b) This causes more cytochrome -c to be released
c) As a result, Apoptosome form more often
d) So, Apaf-1place an important role in causing brain cell death in Alzheimer's disease (Li, P., et al. 1997, Johnson, C.E., et al. 2005).

2.5 Calcium Dysregulation:

Calcium is very important for brain cell communication, but too much calcium inside a cell can cause the cell to die.

a) Amyloid-beta proteins disturb the normal balance of calcium in cells
b) Some receptors (NMDA receptors) become over active and let in too much calcium
c) Too much calcium harms the mitochondria (the cells energy center)
d) This damage makes mitochondria release cytochrome-c
e) Cytochrome-c then turns on enzymes (caspases) that leads to cell death
f) So, calcium imbalance connects Amyloid – beta toxicity to brain cells death in Alzheimer's disease (Mattson 2007, Bezprozvanny & Mattson, M.P. 2008).

2.6 Oxidative stress (Reactive oxygen species-ROS):

Oxidative stress plays a major role in Alzheimer's disease pathogenesis and apoptosis regulation.
Effects: -

a) Damage DNA, proteins, and lipids
b) Impair mitochondrial function
c) Activate p53 and pro- apoptotic pathways
d) Trigger mitochondrial permeability transition
e) Neurons are particularly vulnerable because of high oxygen consumption and lipid rich membranes. Chronic oxidative stress therefore strongly promotes apoptosis in Alzheimer's disease (Markesbery, W.R. 1997, Butterfield, D.A., & Sultana, R. 2007).

2.7 Neuroinflammatory cytokines:

Neuroinflammation is hallmark of Alzheimer's disease.

a) Bind to neuronal death receptors
b) Activates caspases-8
c) Trigger the extrinsic pathway
d) Can also activate the mitochondrial pathway via Bid cleavage (Heneka, M.T., et al. 2015, Calsolaro, V., & Edison, P. 2016).

Table:1

Regulators	Type / Category	Key Component / Examples	Mechanism in Apoptosis	Role in Alzheimer's Disease
Bcl-2 family proteins	Central regulators of intrinsic (mitochondrial) pathway.	Anti apoptotic: Bcl-2, Bcl – XL	Stabilize mitochondrial outer membrane and prevent release of cytochrome – C, thereby inhibiting apoptosis.	Expression often reduces in AD, making neurons more susceptible to apoptosis.
Caspase	Execution regulators of apoptosis	Inhibitors: caspase-8 (extrinsic), caspase-9 (intrinsic); Executioner; caspase -3, caspase-6, caspase-7	Activated caspases cleave cellular proteins and triggers apoptosis processes	Caspase-3 activity is elevated in AD brain, causing DNA fragmentation, neuronal shrinkage and death
P53 (Tumor suppressor protein)	Stress activated apoptotic regulators	P53 protein	Activates pro- apoptotic proteins (e.g. Bax) and suppresses Anti- apoptotic proteins (e.g. Bcl-2)	DNA damage and cellular stress activate P53, shifting balance towards neuronal apoptosis in AD
Apaf-1 (Apoptotic protease activating factor-1)	Apoptosome formation regulators	Apaf-1 protein	Combines with cytochrome-C and pro caspase-9 to form the apoptosome, initiating caspase cascade	Mitochondrial dysfunction in AD increase cytochrome-C release, leading to frequent apoptosome formation
Calcium dysregulation	Cellular signaling imbalance	Excess intracellular calcium, NMDA receptor over activation	Excess calcium damages mitochondrial and promotes cytochrome-C release, activating caspases	Amyloid-β disrupts calcium homeostasis, linking toxicity to neuronal apoptosis
Oxidative stress (ROS)	Cellular damage	Reactive oxygen species	Damages DNA, proteins, and lipids; impairs mitochondria, activates pro apoptotic pathways including P53	Neurons are highly vulnerable due to high oxygen consumption and lipid – rich membranes; promotes chronic neuronal

				death in AD
Neuroinflammatory cytokines	Inflammatory apoptosis regulators	Cytokines released during neuroinflammation	Bind to neuronal death receptors, activates caspase-8 and trigger the extrinsic apoptotic pathways	Neuroinflammation in AD activates both extrinsic apoptosis and mitochondrial pathways through Bid cleavages

3 Disease Implications:

Alzheimer's disease refers to the wide - ranging effects of the disease on the brain, body, daily functioning and society. Alzheimer's is a progressive neurodegenerative disorder, so its implications worsen over time (Alzheimer's Association 2022, World Health Organization 2021).

Neurological Implications:

a) Progressive neuron loss:

Alzheimer's disease causes gradual death of neurons, especially in the hippocampus and cortex (areas for memory and thinking).

b) Brain atrophy:

Shrinkage of brain tissue occurs as the disease advances.

c) Amyloid plaques and tau tangles:

Abnormal protein deposit disrupt communication between neurons and trigger cell death.

d) Neuro transmitter deficits:

Reduced acetyl choline affects memory and learning (Serrano-Pozo, A., et al.2011, Hyman, B.T., et al. 2012).

Cognitive Implication:

a) Memory impairment:

Especially recent (short term) memory.

b) Languages problems:

Difficulty finding words or understanding speech.

c) Disorientation:

Confusion about time, place and peoples
Poor judgement and decision making
Reduced problems solving ability (Salmon, D. P., & Bondi, M.W. 2009).

Behavioral and physiological implication:

a) Depression and anxiety
b) Agitation and aggression
c) Hallucination or delusions (in some cases)
d) Sleep disturbances (Lyketsos, C.G., et al. 2011)

Functional and physical implications:

a) Difficulty with basic task (eating, dressing, bathing)
b) Loss of motor coordination
c) Swallowing problems (late stage)
d) Increased risk of infection (like pneumonia) (Alzheimer's Association. 2022, Mitchell, S.L., et al. 2009).

Social implications:

a) Social withdrawal
b) Communication difficulty
c) Isolation from friends and family
d) Stigma related to dementia (Werner, P., & Heinik, J. 2008).

Economic and societal implications:

a) High health care costs
b) Long term care needs
c) Loss of productivity
d) Emotional and financial burden on families
e) Growing public health challenge due to aging population (Alzheimer's Association. 2022, Wimo, A., et

al.2017).

Disease progression implications:

a) Chronic
b) Progressive
c) Currently incurables
d) Ultimately fatal (often due to complications like infection) (Alzheimer's Association. 2022, World Health Organization. 2021).

4 Treatment of Alzheimer's disease:

a) Current Alzheimer's treatment temporarily improves symptoms of memory loss and problems with thinking and reasoning.
b) These Alzheimer's treatments boost the performance of chemicals in the brain that carry information from one brain cell to another. They include cholinesterase inhibitors and N- methyl D- aspartate antagonists. However, these treatment does not stop the underlying and death of brain cells. As more cells die, Alzheimer's disease continues to progress.
c) Further Alzheimer's treatments may include a combination of medicines. This is similar to treatments for many cancers or HIV/AIDS that include more than one medicine (Alzheimer's Association. 2022).

4.1 Cholinesterase Inhibitors:

A person with Alzheimer's disease has reduced amounts of the neurotransmitter acetylcholine in their brain. Acetylcholine is used to transmit signals between nerve cells. In order to cure memory problems, cholinesterase Inhibitor work by increasing the availability of acetylcholine during synaptic neurotransmission. Galantamine, Donepezil and Rivastigmine are the three cholinesterase inhibitors now being used as first line of therapy for mild to severe Alzheimer's disease. Galantamine inhibit both Acetylcholine and Butyrylcholinesterase, in contrast to donepezil and Rivastigmine, which are both selective inhibitors. No Improvement in everyday activities and behavior was found in a Meta- analysis that include 13 randomized, double blinds studies that were conducted to assess the efficacy and safety of cholinesterase inhibitors (Birks, J. 2006, National Institute on Aging. 2022).

4.2 N- methyl D- aspartate Antagonists:

Alzheimer's disease that is mild to severe can be effectively treated with the non- competitive N-methyl D-aspartate receptor antagonist memantine. The reduction of glutamate induced excito toxicity is achieved modulating N- methyl D- aspartate receptors. A 28- weeks, double- blind parallel group study that demonstrated its advantages revealed that the medication markedly decreased patient deterioration. The majority of pharmacological side effect were mild and through to be unrelated to the drug. Patient behavior improved as a result an improvement in cognitive performance, which led to fewer agitated patient and less requests for care assistance.

For those with intermediate Alzheimer's disease who are unable to take cholinesterase inhibitor medications due to adverse effect, national institute for healthcare and excellence also suggest memantine (McShane, R., et al. 2006, National Institute for Health and Care Excellence. 2021).

4.3 Taking Aim at Plaques:

Some of new Alzheimer's treatments target clumps of the protein beta amyloid known as plaques, in the brain. Plaques are a characteristics sign of Alzheimer's disease (Sevigny. J., et al. 2016, Budd Haeberlein, S., et al. 2022).

Strategies aimed at beta amyloid include:

a) Recruiting The Immune System:

Medicine known as monoclonal antibodies may prevent beta- amyloid from clumping into plaques. They also may remove beta amyloid plaques that have formed. These medicines mimic the antibodies your body immune system's response to foreign invaders or vaccines.

The U.S. Food and drug Administration (FDA) has approved Lecanemab (Leqembi) and donanemab for people with mild Alzheimer's disease and mild cognitive impairment due to Alzheimer's disease.
Clinical Trial found that the medicines slowed declines in thinking and functioning in people with early

Alzheimer's disease. The medicine prevents amyloid plaques in the brain from clumping.

The monoclonal antibody solanezumab did not show benefits for individual with preclinical, mild or moderate Alzheimer's disease. Solanezumab did not lower beta- amyloid in the brain, which may be why it was not effective (van Dyck, C.H., et al. 2023, Honig, L.S., et al. 2018).

b) Preventing Destruction:
A medicine initially develops as a possible cancer treatment- saracatinib is now being tested in Alzheimer's disease. In mild saracatinib turned off a protein that allowed synapses to start working again. Synapses are the ting spaces between brain cells through which the cells communicate.

The animal study experienced a reversal of some memory loss. Human trials for saracatinib as a possible Alzheimer's treatment are now underway (Kaufman, A.C., et al. 2015, Alzheimer's Association. 2023).

c) Production Blockers:
This therapy may reduce the amount of beta amyloid formed in the brain. Research has shown that beta amyloid is produced from a "parent protein" in two steps performed by different enzymes.

Several experimental medicines aim to block the activity of these enzymes. They are known as beta and gamma secretase inhibitors. Recent study shows cognitive decline. They also were associated with significant side effect in those with mild or moderate Alzheimer's. This has decrease enthusiasm for the medicines (De Stropper, B., et al. 2010, Egan, M.F., et al. 2018).

d) Keeping Tau from Tangling:
A vital brain cell transport system collapses when a protein called tau twists into tiny fibers. These fibers are called tangles. They are another common change in the brain of people with Alzheimer's. Researchers are looking at a way to prevent tau from forming tangles. Tau aggregation inhibitor and tau vaccines are currently being studied in clinical trials (Lee, V. M., et al. 2011, Sigurdsson, E.M. 2018).

e) Reducing inflammation:
Alzheimer's causes chronic, low- level brain cell inflammation. Researchers are studying way to treat the processes that lead to inflammation in Alzheimer's disease. The medicine sargramostim (leucine) is currently in research. The medicine may stimulate the immune system to protect the brain from harmful proteins (Heneka, M.T., et al. 2015, Calsolaro, V., & Edison, P. 2016).

f) Researching Insulin Resistance:
Studies are looking into how insulin may affect the brain and brain cell function. Researchers are studying how insulin changes in the brain may be related to Alzheimer's.
However, a trial testing of an insulin nasal spray determined that the medicine was not effective in slowing the progression of Alzheimer's (Craft, S. et al. 2012, Swerdlow, R. H., et al. 2017).

g) Hormones:
Studies during the 1990s suggested that taking hormone replacement therapy during perimenopause and menopause lowered the risk of Alzheimer's disease. But further research has been mixed. Some studies found no cognitive benefit of taking hormone replacement therapy. More research and a better understanding of the relationship between estrogen and cognitive function are needed (Shumaker, S.A. et al. 2003, Maki, P.M., et al. 2019).

5 Lifestyle intervention for Alzheimer's disease:
a) Physical exercise:
Regular aerobic exercise (e.g., walking, jogging, cycling) can improve cognitive function and reduce risk decline. Resistance training and balance exercise can also be beneficial (Lautenschlager, N.T., et al. 2008, Erickson, K.I., et al. 2011).

b) Cognitive training:

Engage in mentally stimulating activities (e.g., puzzles, games, learning new skills) to build cognitive reserve. Cognitive training programs can target specific cognitive domain (e.g., memory, attention) (Ball, K., et al. 2002, Willis, S.L., et al. 2006).

c) Diet and nutrition:
Mediterranean diet rich in fruits, vegetable, whole grain and healthy fats (e.g., omega-3 fatty acid) may support cognitive health. Limit processed foods, sugar and saturated fats (Scarmeas, N., et al. 2006, Morris, M.C., et al. 2015).

d) Sleep And Relaxation:
Prioritize good sleep hygiene (7-8 hours/night) to support cognitive function. Establish a relaxing bedtime routine (Xie, L., et al. 2013, Mander, B.A., et al. 2016).

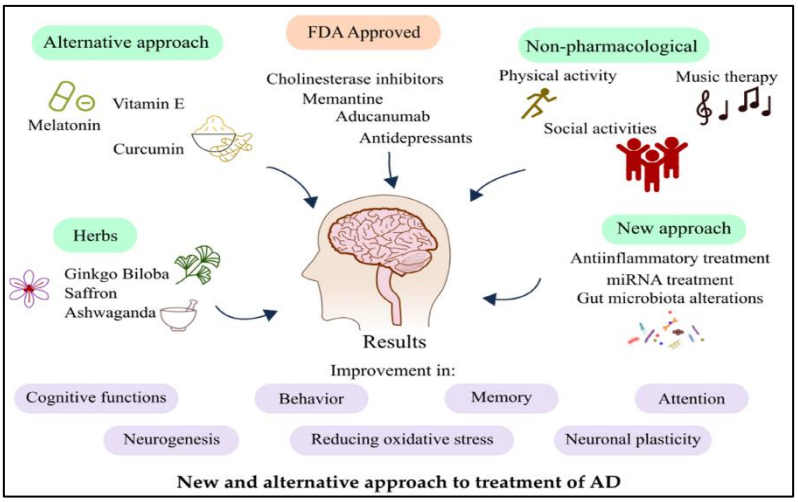

Figure: 5

5.1 Benefits:
a) Potentially good cognitive decline
b) Improve quality of life
c) Reduce risk of progression

6 CONCLUSION:
Alzheimer's disease (AD) is a progressive and ultimately fatal neurodegenerative disorder characterized by gradual neuronal loss, synaptic dysfunction and cognitive decline, in which apoptosis plays a central and decisive role. Apoptosis, a tightly regulated and energy – dependent form of programmed cell death, is essential during neural development for refining synaptic connection and maintaining homeostasis; however, in Alzheimer's disease, this normally protective mechanism becomes dysregulated and contributes to pathologic neuronal loss. The disease is marked by the accumulation of amyloid-beta(Aβ) plaques and hyperphosphorylated, Tau tangles, mitochondrial dysfunction, oxidative stress, calcium imbalance and chronic neuroinflammation, all of which converge to activate intrinsic(mitochondrial) and extrinsic (death receptor) apoptotic pathways. In the Intrinsic pathway, Aβ toxicity and Tau pathology impair mitochondrial function, increase reactive oxygen spices (ROS) production, reduced ATP synthesis, and disturb calcium homeostasis, leading to mitochondrial outer membrane permeabilization and the release of cytochrome-C. This event triggers apoptosome formation through Apaf-1, activates caspase-9 and ultimately stimulates caspase-3, the key executioner caspase responsible for DNA fragmentation, cytoskeletal breakdown and neuronal death. Simultaneously, chronic neuroinflammation- driven by activated microglia and astrocytes- releases cytokines such as TNF-α and Fas ligand that stimulate death receptors, forming the death- inducing signaling complex (DISC) activating, caspases-8, and further amplifying apoptotic cascades either directly or via mitochondrial cross talk through bid cleavage. Central regulators such as the Bcl-2 family protein determine neuronal fate by controlling mitochondrial membrane permeability in Alzheimer's disease, reduced anti- apoptotic protein (Bcl-7, Bcl-Xl) and increased pro apoptotic protein (Bax, Bak, Bad) shift the balance toward cell death. Additional modulators p53, Apaf-1 oxidative stress mediator,

calcium dysregulation, inflammatory cytokines intensify apoptotic signaling, making neurons- already vulnerable due to their high metabolic demand and post- mitotic nature-particularly susceptible to degeneration. The cumulative effect of these molecular event leads to progressive neuron loss in the hippocampus and cortex, resulting in memory impairment, language difficulties, disorientation, poor judgment, behavioral disturbances etc.

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