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ADVANCE IN THE PHARMACOLOGICAL MANAGEMENT OF ALZHEIMER DISEASE CURRENT THERAPIES AND FUTURE PROSPECT

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ABSTRACT

Alzheimer's disease (AD) is the main cause of dementia and a major worldwide health concern. Its clinical features include progressive memory loss, cognitive deterioration, and aberrant conduct. Pathologically, AD causes synaptic dysfunction, neuronal degeneration, and brain atrophy through the accumulation of amyloid-β plaques and neurofibrillary tangles composed of hyperphosphorylated tau protein. Current treatments, such as memantine and cholinesterase inhibitors, only slightly reduce symptoms and do not stop the disease's progression. As a result, extensive research is being done to find new treatment approaches that focus on the fundamental causes of AD. Emerging approaches include anti-amyloid and tau-directed therapies, modulation of neuroinflammation, and interventions aimed at restoring mitochondrial function. In parallel, lifestyle modifications such as physical exercise and nutritional optimization are being explored for their potential in prevention and disease delay. Forward-looking innovation involving personalized medicine, gene-editing technologies, and stem cell–based therapies may offer transformative benefits in the future. Continued advancements in AD research are crucial for developing effective disease-modifying treatments and improving patient outcomes.

Keywords: Alzheimer's Disease, Life Style Intervention, Cognitive Impairment, Behavioural Distubance, Cholinesterase Inhibitors.

I.Introduction

The most prevalent kind of dementia is called Alzheimer's disease (AD), after the German doctor Alois Alzheimer. It is a gradually progressing neurodegenerative condition marked by neurotic plaques and neurofibrillary There is neuronal loss and/or disease in the entorhinal cortex, hippocampus, amygdala, frontal, parietal, and temporal cortical association areas. Prior to affecting the entorhinal cortex, the hippocampus CA1 region, and the cortical association areas, trans-entorhinal tangles first affect the frontal, parietal, and temporal lobes.

Amyloid-beta peptide (Aβ) buildup in the brain's most damaged region, the medial temporal lobe, and neocortical structures is more closely linked to dementia severity than amyloid plaques (1). AD3 is predicted to impact 2.3 million people in the US overall (range: 1.09-4.8) and is associated with elevated levels of CSF and plasma YKL-40, an indication of astrocytosis and microglial activation. One After the age of 60, the prevalence of AD doubles every five years, rising from 1% in those between the ages of 60 and 64 to up to 40% in those over 85 (2). The patient is usually unaware of memory loss or cognitive impairment, and deficiencies in executive function (planning, insight, and judgment) are common. Over time, all cognitive impairments get worse. Neuropsychiatric symptoms are common in AD. Apathy appears early in the clinical process as a lack of concern and attention. As the illness develops, agitation becomes more common and is a common reason for admission in a nursing home. Delusions affect about 25% of patients, and depression symptoms affect 50% of people (3). If focal abnormalities, gait issues, or seizures appear early in the clinical course of dementia, the diagnosis of AD is unlikely. There are no motor system abnormalities until the latter years of AD (4a). Cerebral disorders like Alzheimer's disease (AD) and other conditions like intoxications, infections, abnormalities in the pulmonary and circulatory systems that reduce the amount of oxygen reaching the brain, nutritional deficiencies, vitamin B12 deficiency, tumours, and others can cause a progressive loss of cognitive abilities (5). Dementia is predicted to affect 78 million people by 2030. Additionally, it is anticipated that the global cost of medical care, social services, and unpaid caregiving for dementia patients will exceed US$2.8 trillion. Families, individuals, and society at large will all be significantly impacted by this circumstance. The most common type of dementia, Alzheimer's disease (AD), has comparable demographic traits and is a significant global problem. With an annual incidence of 1275 new cases per 100,000 people, AD affects roughly one in nine Americans 65 and older (10.8%) (6About 60% of dementias are Alzheimer's dementia (AD), which is the most common subtype within the dementia range. Research on developing medications for primary, secondary, or tertiary dementia prevention has skyrocketed as a result of the aging population and the ongoing growth in life expectancy, which has caused a rapid rise in the number of dementia patients. There are currently no viable pharmacotherapeutic treatments for the prevention and treatment of dementia, including AD and behavioural and psychological symptoms of dementia (BPSD), despite all scientific efforts. This review will concentrate on pharmacological treatments for AD because AD is the subject of the majority of pharmacological research in the field of dementia. First, a brief summary of the current (7). The progression of AD and associated symptoms can be inferred from the following two categories of neuropathological alterations: (1) A positive lesion is the build-up of neuropil threads, dystrophic neurites, amyloid plaques, neurofibrillary tangles, and other deposits in the brains of AD patients. Furthermore, two negative lesions (caused by losses) exhibit significant atrophy as a result of the loss of synapses, neurons, and neuropils. Additionally, oxidative stress, neuroinflammation, and damage to cholinergic neurons might result in neurodegeneration (8).

II.Prevalence

After the age of 60, the prevalence of AD doubles every five years, rising from 1% in those between the ages of 60 and 64 to up to 40% in those over 85 (9). The anticipated total cost of patient care in 1991 was $76.3 billion, of which $20.6 billion came from direct charges. 4. The cost of nursing home care, which is around $47,000 per patient per year, covers the majority of the direct expenditures of care for people with AD (10). In addition to age and female sex, epidemiologic studies have identified other risk factors for AD. The apolipoprotein ~ 4 (APOE} 4) allele is the biggest risk factor. Of its three forms (forms 2, 3, and 4), only the ~ 4 allele raises the risk of AD (11). Although the 4 genotype is a major risk factor for AD, it is not specific or sensitive enough to be utilized as a diagnostic test (12). Variations in AD prevalence between global population groupings point to unknown genetic or environmental factors influencing AD prevalence (13).

III.Pathophysiology

Neuronal loss and/or disease are seen in the entorhinal cortex, hippocampus, amygdala, frontal, parietal, and temporal cortical association areas. Before affecting the entorhinal cortex, the hippocampus CA1 region, and the cortical association areas, trans-entorhinal tangles first affect the frontal, parietal, and temporal lobes. Tangles have a stronger correlation with dementia severity than amyloid (14a). Amyloid plaques and hyperphosphorylated tau are the most frequent causes. Senile plaques are caused by extracellular amyloid accumulation. In addition to disrupting microtubules, hyperphosphorylated tau affects the cytoskeleton and signal transduction pathways in neuronal cells. Additional factors that contribute to the disease's progression include cholinergic insufficiency, oxidative stress, mitochondrial dysfunction, neuroinflammation, and autophagy failure. The presence of macrophages and monocytes in the cerebral cortex activates microglial cells in the parenchyma (15).

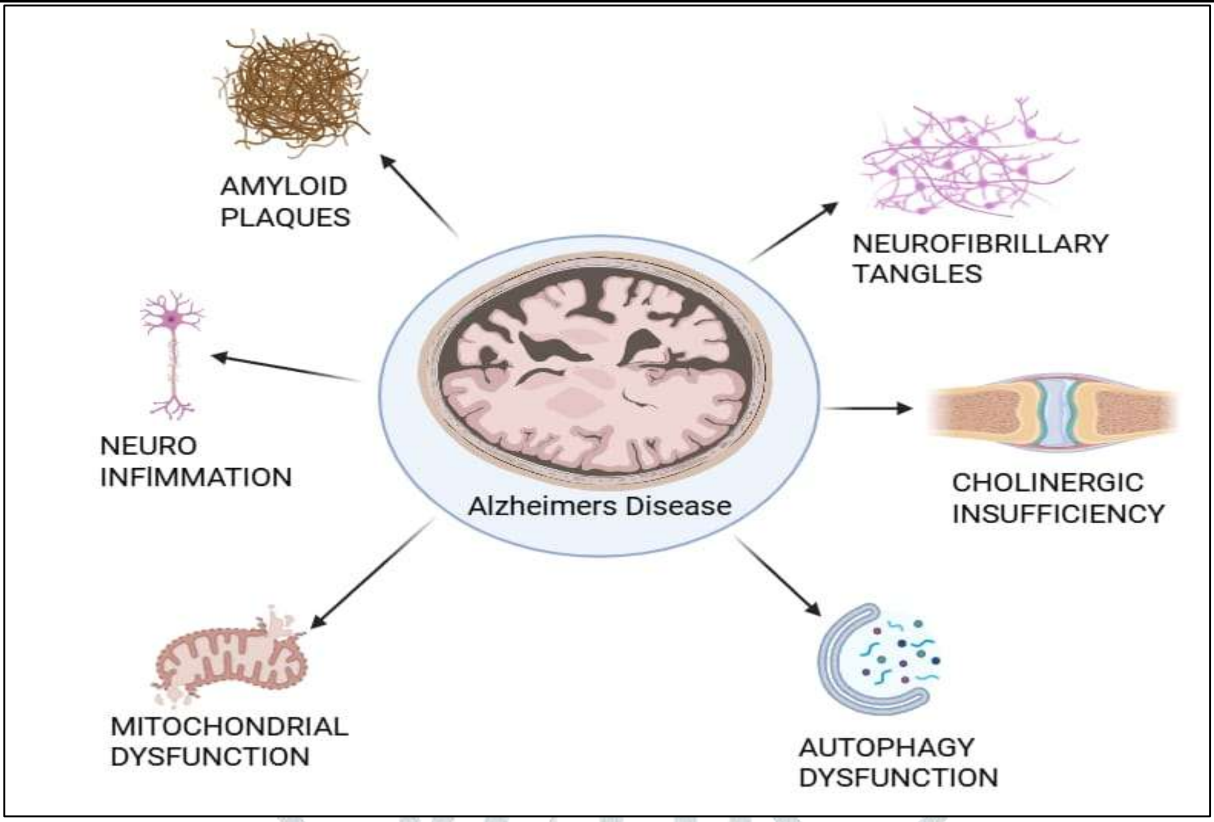

Figure 1. some factors responsible for the progression of Alzheimer's disease

3.1. Amyloid beta pathology biomarkers

One important indicator is the ratio of CSF Aβ42 to Aβ40. The buildup of Aβ plaque in the brain is indicated by a drop in this ratio (164). Translocator protein (TSPO) tracers used in PET imaging reveal neuroinflammation and microglial activation in the AD brain35. Research using PET imaging with amyloid tracers, such as florbetapair, found a correlation between greater brain amyloid deposition and cognitive impairment in patients with low CSF Aβ42 levels (17). Amyloid PET Imaging: PET tracers such as 11C-PiB (Pittsburgh compound B) help differentiate AD from other dementias by showing amyloid accumulation in vivo. (18). Total tau (t-tau) and phosphorylated tau (p-tau) in CSF:
While increased t-tau denotes neuronal injury, elevated p-tau is linked to NFT disease (19).

3.2. Tau pathology biomarkers

Elevated CSF p-tau levels were utilized as a predictive diagnostic in MCI patients and were linked to rapid cognitive impairment (20). Tau PET Imaging: To map the spread of tau pathology in AD patients, second-generation tau PET tracers like flortaucipir are being used more and more (21).

3.3 Neurodegeneration biomarkers

Elevated levels of neurofilament light chain (NfL) in blood and CSF are indicative of axonal injury and neurodegeneration in AD and other neurodegenerative illnesses (22a). MRI-derived measures of atrophy: The gold standard for evaluating neurodegeneration is structural magnetic resonance imaging (MRI), which can identify hippocampal shrinkage.

3.4. Neuroinflammation biomarkers

AD3 is associated with elevated levels of CSF and plasma YKL-40, a marker of astrocytosis and microglial activation (4b). TSPO PET Imaging: Using translocator protein (TSPO) tracers, PET imaging shows neuroinflammation and microglial activity in the AD brain (23).

3.5. Hyperphosphorylated Tau Protein and Aβ Hypothesis

One of the pathologic characteristics of AD is the production of SP by Aβ deposition. When APP is broken down by γ-secretase, a soluble micro peptide called Aβ is produced. Depending on the severity, it may result in harmful oligomers such protofibrils, fibrils, or plaques, oligomerization. Although the etiology of AD is unknown, the stability, concentration, and sequence of Aβ are all critical for its development. On the other hand, tau phosphorylation controls the stability and polymerization of microtubules, which are facilitated by the protein tau. AD is caused by a number of mechanisms, such as abnormal APP metabolism and improper amyloid clearance, which lead to hyperphosphorylated tau-mediated microtubule disintegration and synapse failure(24a).

3.6. oxidative stress conditions

Reactive oxygen and nitrogen species, or ROS and RNS, are produced by many human processes, both healthy and unhealthy. They can both positively and negatively affect cellular signaling pathways, as well as damage biological components such proteins, lipids, DNA, and cell membranes. Because the brain utilizes 20% more oxygen than other respiratory tissues of mitochondria, it is particularly vulnerable to oxidative stress. A variety of polyunsaturated fatty acids are found in neurons, the brain's fundamental functional unit. Furthermore, oxidative stress damage results from glutathione deficiency in neurons (25).

3.7. cholinergic theory

In individuals with Alzheimer's disease (AD), the APOE genotype affects the effectiveness of AChEIs. AChEI medications are crucial for the treatment of AD, and the APOE genotype is believed to be the most significant risk factor. Since the "Cholinergic Theory" of AD was developed in 1976, it has been recognized that cholinergic neurons are not the primary target of the disease. In individuals with mild to moderate Alzheimer's, a reduction in cholinergic receptor binding in several brain regions results in neuropsychiatric symptoms. This decline in receptor binding may be associated with slower processing rates in older persons. For nearly 20 years, donepezil and cholinesterase inhibitors (ChEIs) have been used to treat AD symptoms (26). By binding to AChE and preventing ACh's reversible breakdown, donepezil increases ACh levels at synapses. The mild, temporary cholinergic side effects of this often-prescribed drug very slightly affect the digestive and neurological systems (27a).

3.8. Amyloid Cascade Theory

According to the amyloid cascade theory, abnormal amyloid-beta (Aβ) plaque deposition in numerous brain areas is the source of neurodegeneration in AD.
Furthermore, in silico research improved our comprehension of how Aβ degrading enzymes identify and degrade Aβ peptides. Computational research will therefore provide a wealth of reasonably reliable information regarding the potential of Aβ-degrading enzymes as a therapeutic target. The amyloid idea has gained strength during the last 20 years, particularly due to genetic research (28b).

3. 9. Glutamatergic/Excitotoxicity Hypothesis.

Through its receptors, especially the N-methyl-D-aspartate (NMDA) type, and by interacting with other brain regions like cholinergic neurons, the neurotransmitter glutamate contributes to complex brain activities including learning and memory (29).

3.10. Inflammatory Hypothesis.

The development of the central nervous system (CNS) depends on the inflammatory responses of astrocytes and microglia (30). Chemokines and pro-inflammatory cytokines including TNF-α, IFN-γ, and IL-1β are typically produced and secreted when microglia are stimulated. These cytokines then increase the creation of Aβ42 and its distribution throughout the central nervous system by stimulating the synthesis of Aβ42 oligomers through local astrocyte-neuron connections(14b).

3.11. Neurodegeneration biomarkers

Increased levels of neurofilament light chain (NfL) in blood and CSF are a sign of axonal injury and neurodegeneration in AD and other neurodegenerative illnesses (22b). Atrophy Measures Derived from MRI: The gold standard for evaluating neurodegeneration is structural magnetic resonance imaging (MRI), which can identify hippocampus atrophy (16b).

3. 12. Neuroinflammation biomarkers

AD is associated with elevated levels of CSF and plasma YKL-40, a marker of astrocytosis and microglial activation. PET imaging with TSPO: PET imaging uses translocator protein (TSPO) tracers to show neuroinflammation and microglial activity in the AD brain (24b).

3.13. Aβ

It is mostly present at neural synapses and is necessary for brain development, synaptic plasticity, and the brain's intrinsic immune system. Once produced by neurons, APP can be broken down by proteases. The α-decomposition pathway and the β-catabolic pathway are the two primary decomposition pathways. The β-catabolic route, which is controlled by the enzyme β-secretase (BACE1), is the only pathway that can produce Aβ Very low quantities of β-amyloid are maintained in a normal organism.The individual molecules of Aβ are called Aβ monomers, and they eventually group together to form Aβ oligomers. Oligomers of Aβ are extremely neurotoxic (31). Apolipoprotein E4 (APOE 4) has been identified as the primary genetic risk factor for late-onset AD because it may impede Aβ clearance and promote Aβ buildup in the brain. Post-translational modifications to essential proteins during Aβ processing also have a major impact on the pathophysiology of AD. Increased BACE1 SUMOylation has been demonstrated to be a key factor in the pathophysiology of AD (32). The primary techniques for identifying Aβ are now cerebral amyloid PET imaging and the reduction of Aβ42 in cerebrospinal fluid (CSF). To increase the assay's generalizability, less expensive and minimally invasive blood-based biomarkers have been developed; plasma biomarkers have also been developed for individual-level prediction (33). In light of previous study findings, researchers have shifted their attention from the direct role of Aβ in the pathophysiology of AD to tau proteins (34).

3.14. Tau

The generation of hyperphosphorylated, self-aggregating tau (commonly called p-tau), which is brought on by hyperphosphorylation, is a feature of several tau proteinopathies. In AD, several kinases phosphorylate over thirty tau residues, with GSK3β being the most common (35). context Recent research has shown that plasma p-tau217 is a very effective diagnostic test for AD, especially in patients of atypical dementia or early-onset AD that are assessed by a specialist (36). Normal tau function can be disrupted by mutations in the tau gene. For instance, the ΔK280 mutation can enhance tau's propensity to self-aggregate, decrease tau's capacity to connect with microtubules, and so encourage the development of PHF and NFT (37).

3.15.AD Deteriorates with Aging

The nervous system's axons are encased in a multilayered cell membrane material called myelin. As we age, myelin structure deteriorates. In 2023, scientists discovered that two forms of myelin dysfunction in mice caused by myelin injury increased the formation of Aβ and decreased its elimination. These mice displayed typical signs of behavioral impairments similar to AD (38). Therefore, age-related myelin anomalies may promote the development of Aβ plaques directly or indirectly. This study demonstrates a strong connection between AD and aging. However, it has recently been discovered that pathogenic soluble tau can easily reach primary astrocytes both in vitro and in vivo, and that pathogenic tau transport can cause endogenous astrocyte tau to become phosphorylated, which results in instability of the microtubule cytoskeleton. Additionally, pathogenic tau delivery to astrocytes successfully increased a number of cellular senescence markers, proving for the first time that pathogenic tau causes astrocyte senescence (39).

3.16. Neuroinflammation

Astrocytes and microglia cause neuroinflammation, which is linked to pathology caused by tau and amyloid proteins. The central nervous system's brain-resident immune cells, known as microglia, are activated in reaction to dangers and are crucial for removing Aβ and preserving its dynamic homeostasis (40). The current theory states that in the early stages of AD, Aβ stimulates microglia, which then phagocytose Aβ. However, microglia eventually enlarge and become incapable of processing Aβ. Chronic activation of microglia can continually produce neuroinflammation, which can exacerbate neuronal injury and promote amyloid deposition, by generating pro-inflammatory cytokines (such as IL-1, TNF-α, and IL-6) and toxic metabolites. Increased amyloid accumulation and neuronal cell death may follow from this (41). SASP is experienced by various cell types in AD, leading to the secretion of a range of pro-inflammatory cytokines. Researchers have demonstrated that exogenous NAD+ supplementation reduces pro-inflammatory cytokine production and attenuates astrocyte and microglia activation (42).

3.17. Endothelial Dysfunction

Accelerated apoptosis and poor energy metabolism are two detrimental consequences on endothelial cells. Oxidative stress causes these consequences by altering the BBB's structure and resulting in vascular damage (43). Bai et al., "Oxidative stress: The core pathogenesis and mechanism of Alzheimer’s disease." Aging research reviews 77 (2022): 101619 (50) The degree of BBB degradation can be determined by the blood's soluble platelet-derived growth factor receptor-β, depending on the sickness process (44). Cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1) can be used to detect endothelial dysfunction, vascular endothelial cell damage, and inflammatory response, which can help in early identification and tracking of AD development (45). Therefore, endothelial dysfunction-induced BBB damage exacerbates pathological deposits in the brain by causing neuroinflammation, oxidative stress, and neurotoxicity. As the aging process progresses, endothelial cells gradually degrade, changing morphologically and gradually losing their ability to function normally. This will impact barrier dysfunction, vascular permeability, and endothelium-dependent diastolic capacity, ultimately leading to vascular leakage (46).

3.18. Cholinergic Hypothesis

Cognitive decline, the main symptom of AD, has long been associated with dysregulation of the cholinergic system. Cholinergic neurotransmission mechanisms, which are crucial for certain cognitive processes, are mostly found in the forebrain, nucleus basalis meynert (NBM), and hippocampus (47). By lowering intracellular glucose availability, preventing ACh synthesis, obstructing signal transmission, triggering tau hyperphosphorylation, and causing oxidative stress, this pathway further degrades cognitive performance (48). 18F-FDG Brain hypometabolism in AD patients can be detected by PET, which measures the regional glucose consumption associated with the strength of glutamatergic synapses in local cerebral tissues. It can show the characteristic patterns of AD neurodegeneration in patients with mild cognitive impairment prior to MRI (49). Furthermore, in addition to memory loss and cognitive impairment, cholinergic neuron degeneration causes several other issues. Hypoglycaemia can be detected prior to the onset of AD symptoms (50).

3.19. Glutamatergic Hypothesis

Reduced glutamatergic neuron activity and postsynaptic NMDA receptor expression, which lowers synaptic plasticity, neuronal excitability, and synaptic transmission efficiency, are hallmarks of physiological aging (51). As people age, oxidative stress buildup and neuroinflammation can worsen glutamate reuptake inhibition, induce excitatory neurotoxicity, and hasten the onset of neurodegenerative diseases like AD. By boosting presynaptic glutamate release and disrupting NMDA receptor function, Aβ and hyperphosphorylated tau proteins may worsen this pathogenic process (52). Recent large-scale proteome studies have demonstrated the strongest correlation between cognitive impairment and synaptic proteins unrelated to tau and amyloid proteins (53a). Both the AD and aging processes significantly change the normal state and function of mitochondria(53b).

3.20. Metabolic Dysregulation

For calcium homeostasis and brain metabolism, mitochondria are essential organelles. Significant impairment of mitochondrial energy metabolism occurs in AD, which is characterized by aberrant respiratory chain complex function and decreased activity of important tricarboxylic acid cycle (TCA) enzymes (54). These important enzymes are activated by Ca2+, which causes disruption of homeostasis in AD. Consequently, it causes ATP synthesis to decline (55). The oxidatively phosphorylated mitochondrial electron transport chain (ETC) produces around 90% of the oxygen-dependent ATP needed by brain neurons. As a result, the central nervous system is impacted by oxidative phosphorylation deficiency before any other system (56). Even while mitochondria have defence mechanisms against damage, aging can be made worse by mitochondrial malfunction when these defences are inadequate. Age-related accumulation of mitochondrial DNA (mtDNA) mutations leads to respiratory chain failure and an increase in the production of oxygen free radicals, which in turn leads to the accumulation of additional mtDNA mutations (57). Age-related declines in mitochondrial function are characterized by decreasing quantity, increased size, and decreased membrane potential. The normal physiological activity of cells is impacted by this loss of function, which decreases cellular energy metabolism and accelerates the aging process (58). Both of these circumstances could lead to a reduction in ATP synthesis and an obstruction of the electron transport chain. As previously mentioned, ApoE4 can also interact with mitochondria, resulting in mitochondrial fragmentation and decreasing the potential of the mitochondrial membrane, which impedes the production of energy and causes AD (59).

3.21. Other Factors About Mitochondrial Homeostasis

In recent years, iron death has been found to play a major role in the pathologic process of AD. Iron deficiency is the cause of NFT and senile plaque (SP) deposition.

Together, increased ROS and Aβ enhance the permeability of neuronal membranes, lead to an excess of calcium ions, and cause the potential of the mitochondrial membrane to collapse. Additionally, throughout normal physiological and metabolic activities, mitophagy is essential to mitochondrial function. Mitophagy is a crucial mechanism for eliminating damaged mitochondria. In order to eliminate damaged mitochondria, the PINK1/Parkin pathway normally recognizes the breakdown of the mitochondrial membrane potential and starts ubiquitylation and autophagosome recruitment (60).

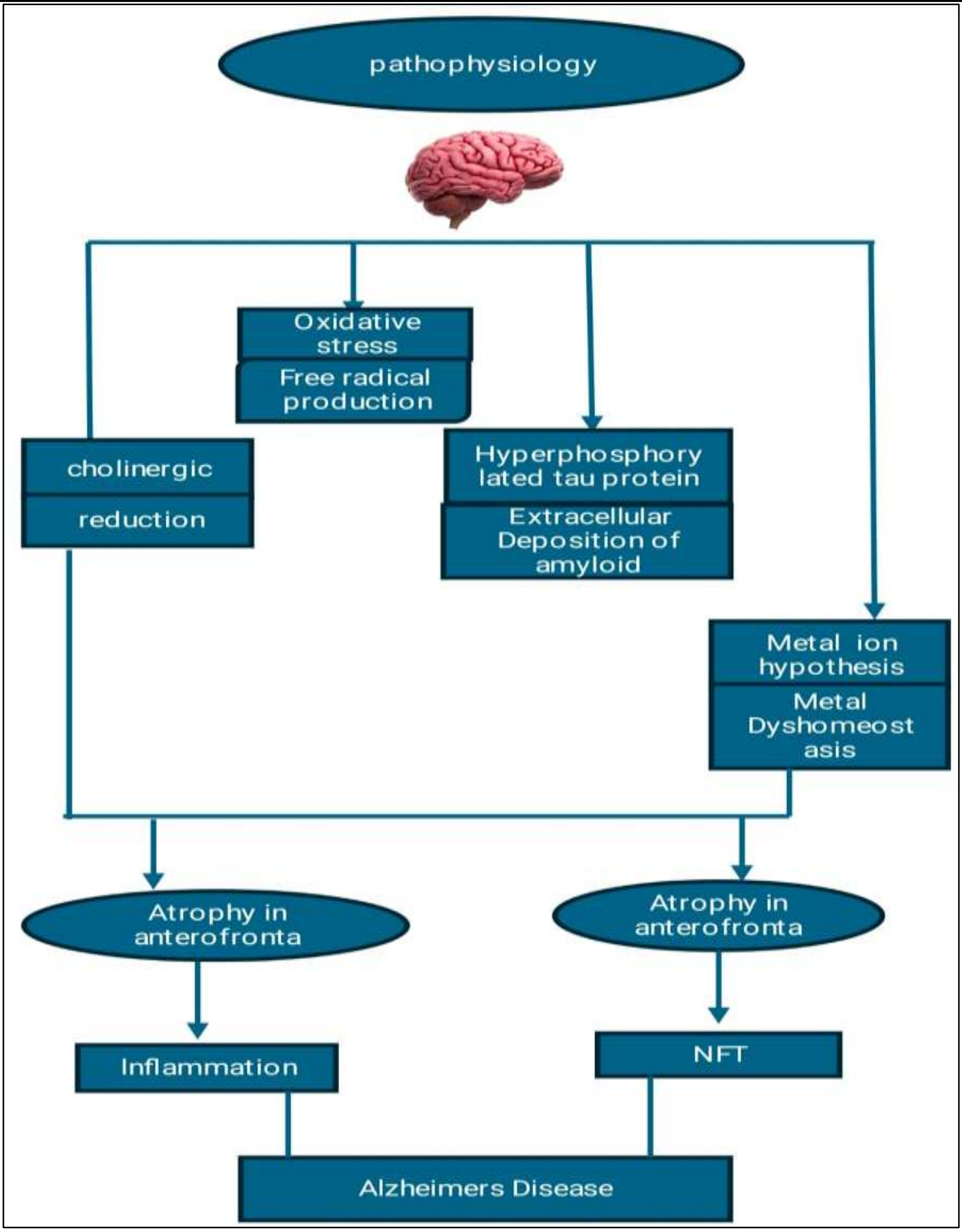

Figure 2. Hypothesis for pathophysiology of Alzheimer's disease.

IV.Clinical sign

Before beginning clinical trials, therapeutic approaches must be validated in model animals. These models provide a controlled experimental framework for studying the origins and treatments of human diseases by simulating physiological and pathological processes. In this overview, we've included a selection of well-known animal models for AD and aging. Anti-inflammatory and antioxidant methods, together with nerve injury restoration, are the main focus of current therapeutic approaches. Furthermore, techniques for mitochondrial-targeted repair, nerve repair by stem cell differentiation, and precisely targeted therapies using gene editing technologies are being investigated. Exercise, a nutritious food, and a healthy lifestyle all support these. Combining treatment strategies with model animals can effectively complete final medication screening and efficacy validation.

4.1 Animal Model of Aging

Prolonged oxidative stress can lead to microglial overactivation and downregulation of synaptic protein expression in D-galactose-induced mice, which in turn induces NLRP3 inflammatory vesicles (61).

4.2. Therapeutic strategies

4.2.1. preclinical strategies

The treatment showed a better safety profile than lecanemab, aducanumab, and donanemab. Exploratory analysis showed a trend toward a decreased rate of cognitive deterioration in the laromestrocel treatment group, despite the trial's primary goal being safety. Larger phase 3 clinical trials may be carried out in the future to verify the importance and long-term safety of the cognitive protective effect (62). Laromestrocel, the first mesenchymal stem cell (MSC) treatment to get to the clinical stage of AD, recently released the results of its phase 2a research. The results show that, when given in single or repeated doses, laromestrocel can assist people with moderate AD address underlying cognitive decline and slow the rate of brain shrinking while maintaining a strong safety profile (63). By activating the Wnt/β-catenin pathway, bone marrow mesenchymal stem cell (BMMSC) transplantation improves memory impairment in the AD animal model (64). The accuracy, stability, and application of gene-editing technologies have significantly improved in recent years. These technologies have enormous potential for aging and AD gene therapy (65). Stem cells, on the other hand, have a great potential for differentiation and, depending on the kind, can aid in the healing of nerve damage. Preclinical treatments use precise gene-editing methods and stem cells with improved differentiation potential to deliver restorative therapy. By changing APOE4 to APOE3, gene-editing technology can lower the hereditary risk of AD by focusing on the APOE gene, a major genetic risk factor for the disease (66).

4.2.2. Intervention

According to a recent study by Brandao et al., xenon (Xe) can reduce inflammation and amyloidosis and stop microglia activation in AD. This was demonstrated using the mouse models 5xFAD and APP/PS (67).

Intervention strategies centered on antioxidants and their dynamic equilibrium have been investigated from the standpoint of mitochondrial biological activities and processes in order to take advantage of the therapeutic potential of targeting mitochondria. Mouse models have been used in a sizable number of pharmacological research projects and therapeutic strategies to date. Studies have indicated that CoQ10, an antioxidant, can lessen oxidative damage brought on by mitochondrial dysfunction in AD; nevertheless, more research is required to confirm its therapeutic effectiveness. As an analog of CoQ10, idebenone is capable of efficiently scavenging a range of free radicals (68). According to recent research, it is possible to prevent the amyloid-dependent drop in β-protein-positive interneurons, restore myelin equilibrium, and reverse the loss of mature oligodendrocytes by genetically inhibiting IL-12 transmission. According to this study, neuroinflammation could be a helpful therapeutic target and intervention for AD (69). Furthermore, supplementing with betaine or folic acid can improve AD's metabolic buffering ability and reduce inflammation (70). Many Chinese herbal remedies, including iguanodine and bovine cerebroside, can have synergistic anti-inflammatory effects by simultaneously blocking the NLRP3, NF-κB, and MAPK pathways (71). Furthermore, Ebselen can enhance mitochondrial function by preventing the development of the mitochondrial permeability transition pore (mPTP). In an AD mouse model, ebselen can also reduce neuroinflammation and enhance synaptic function, learning memory, and mitochondrial bio competence (72). Therefore, NAC may be able to lessen poor energy metabolism and mitochondrial oxidative stress in AD through similar mechanisms. This also holds true for PPARγ/PGC-1αagonists like pioglitazone (73). Apelin-13 may activate mitochondrial biosynthesis and have neuroprotective effects via the PPARγ/PGC-1α-signalling pathway (74). Mdivi-1 is a mitochondrial division inhibitor. Mdivi-1 can reduce mitochondrial fragmentation and improve neuronal survival in AD models where neuronal damage is closely associated with an imbalance in mitochondrial division and fusion (75).

V.Potential targets

Finding new therapeutic targets creates opportunities for creating AD-addressing therapies. Numerous strategies are being investigated by researchers, such as the creation of tiny compounds, antibodies, and genes treatments, as well as reusing already-approved medications. With clinical trials being carried out to assess the efficacy and safety of various medicines, there is hope for the future of managing Alzheimer's disease. Here is a list of AD-targeting drugs and the routes they affect (76).

(a) Cholinesterase Inhibitors

The symptoms of Alzheimer's disease are often treated using a class of drugs called cholinesterase inhibitors. These medications work by increasing the brain's levels of acetylcholine, a neurotransmitter crucial to memory and learning. By stopping the enzyme acetylcholinesterase from degrading acetylcholine, cholinesterase inhibitors help people with Alzheimer's disease think more clearly (77).

1. Donepezil (Aricept)

One of the most often recommended medications for AD is donepezil. It comes in a range of strengths and is usually well tolerated. Donepezil increases cholinergic neurotransmission in the brain by blocking acetylcholinesterase. The medication is mostly used to treat mild to moderate AD, while it may potentially help with more severe instances (78).

2. Rivastigmine (Exelon)

Another cholinesterase inhibitor that has been shown to be effective in treating Alzheimer's disease is rivastigmine. Both patch and pill versions are available. Rivastigmine improves cognitive function by preventing acetylcholine breakdown. The majority of its uses are for mild to moderate AD (79).

3. Galantamine (Raza dyne)

Galantamine is prescribed for mild to moderate AD and is a cholinesterase inhibitor with allosteric modulatory effects on nicotinic acetylcholine receptors. This dual mechanism of action may offer additional benefits for cognitive function (80).

VI.Current therapy and upcoming treatment: -

Early Alzheimer disease-related cognitive impairments are hard to differentiate from those linked to aging normally. the case discussion that goes with it offers a method for assessing memory loss. In the sections that follow, we go over recent and upcoming diagnostic laboratory research (81).

1.A sincere and successful exchange of information and feelings between the patient, physician, and caregiver will enable prompt symptom recognition, accurate evaluation and diagnosis, and suitable guidance.

2. Behavioural strategies: - Regularity and simplification of the environment10; - Routines10; - Communication strategies like peaceful exchanges, providing entertaining activities, speaking plainly, and "saying no" only when safety is at risk10; Timely preparation for medical and legal requirements and judgments 10; - Cognitive behavioral therapy; - Exercise, light, and music therapy (82).

memantine can be used for those with mild to severe dementia. Galantamine, memantine, donepezil, and rivastigmine are the main medications that have been approved. But only when prescribed at the right moment do they enhance quality of life (83).

4. Testosterone: Whether testosterone benefits males with Alzheimer's disease is unknown. It's possible that the improvement in visuospatial cognition seen in two double-blind, randomized, placebo-controlled experiments isn't clinically significant. 46, 47 3. Cholinesterase inhibitors can be used for patients with AD at any stage, and The effects of giving men with mild to moderate Alzheimer's disease 75 mg of 1% testosterone gel every day for six months were investigated in a randomized, placebo-controlled study. 48. Although there were no statistically significant improvements, patients' quality of life did marginally increase. Men over 65 with low testosterone levels and restricted mobility participated in a randomized, double-blind, placebo-controlled study comparing testosterone gel with a placebo (84).

5. Although its exact mode of action is unknown, memantine, an uncompetitive NMDA receptor modulator, may prevent glutamate-mediated neurotoxicity, which occurs when neurons die during AD. A meta-analysis supports memantine's effectiveness in treating moderate-to-severe AD on measures of cognition, activities of daily living (ADL), and neuropsychiatric symptoms. Similar to ChEI, the drug has virtually little effect on the long-term course of the illness. It is not advised to give the medication to people with mild AD because of its limited effects in mild-to-moderate stage AD (85).

6. Patients and researchers experienced a setback when antiamyloid failures occurred often, but they also improved inclusion criteria and allowed for an early identification of AD. But as of January 2022, no antiamyloid antibody treatment—including aducanumab, which the FDA recently approved—had effectively achieved the clinical endpoint in phase 3 research. Antiamyloid antibodies, including gantenerumab, lecanemab, and donanemab, which selectively bonded to aggregated Ab in preclinical investigations, are undergoing phase 3 trials. These most recent antiamyloid antibodies have continuously demonstrated the elimination of brain Ab in amyloid PET imaging studies and have improved primary cognitive results in phase 2 research. Taking aim at mitochondrial malfunction Ab buildup increases the formation of ROS and decreases complex IV activity by blocking specific mitochondrial import channels. Further inducing mitochondrial malfunction and ultimately resulting in cell death is the increased generation of ROS by the mitochondria (86).

7. Enzyme known as beta-secretase

CSF beta-amyloid levels have been shown to be lower in small molecule beta-secretase inhibitors than in controls. MK-8931 and AZD3293 are two agents undergoing phase II/III clinical studies (87).

VII.Future strategies

Due to AD's complexity, treatment approaches may need to be equally sophisticated. Early sickness detection, combination therapy, and lifestyle modifications likely have an impact on the pathology's successful elimination. Poor diet can increase the risk of acquiring a disease, according to a substantial body of evidence. There is no doubt that maintaining a healthy diet will help you prevent AD.

However, neither the antioxidant diet nor the Mediterranean-style diet can prevent or delay AD on their own. We believe that combination medications that target many AD pathways in addition to carefully thought-out dietary regimens are the way forward (88).

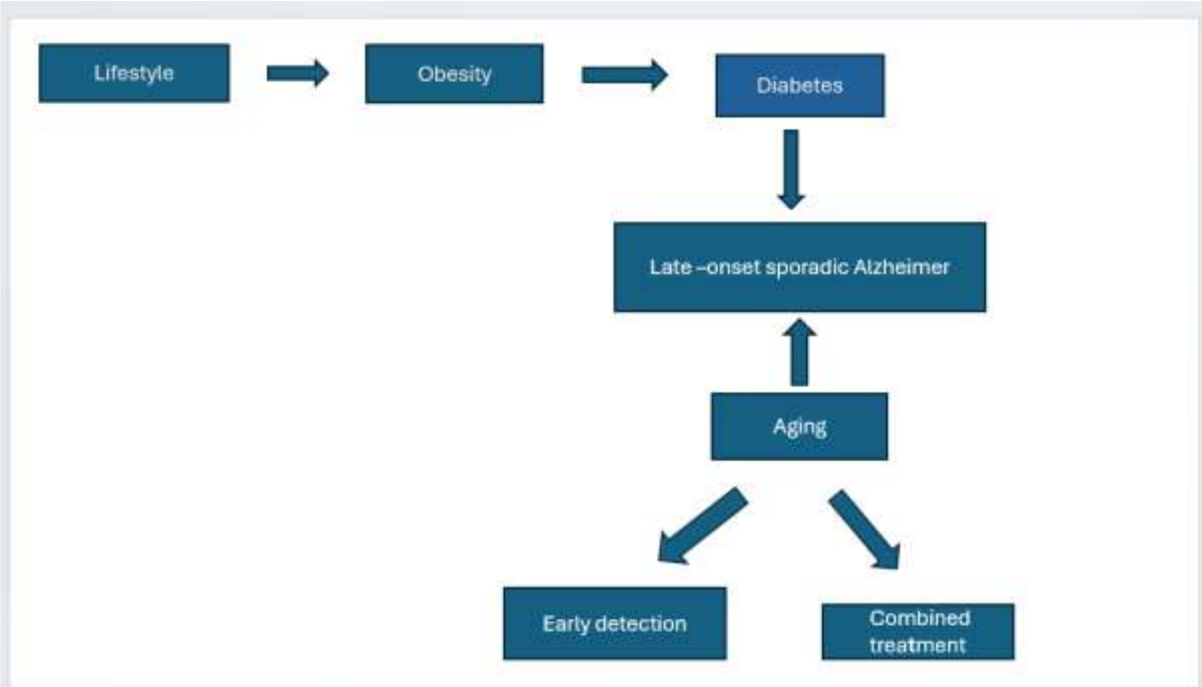

Figure 3. systematic strategies of Alzheimer disease

VIII.Clinical trials

8.1. Dimebon

Dimebon concurrently inhibits the NMDA receptor and cholinesterase. Dual blockade might improve the effectiveness of AD treatment (89). In Russia, 183 individuals with mild to severe Alzheimer's disease participated in a 6-month, randomized, double-blind, placebo-controlled experiment using Dimebon. Assessments of cognitive function, memory, daily living skills, global function, and behaviour were among the primary and secondary goals. According to results released by the pharmaceutical company "Medivation" in September 2006, Dimebon significantly outperformed a placebo in all five efficacy endpoints. Patients receiving dimebon showed a notable increase in memory, global function, cognition, daily living activities, and behavior when compared to placebo. Results have not yet been released, despite these encouraging reports (90).

8.2.DNA

Epidemiological studies have linked a lower incidence of AD to increased consumption of the omega-3 (n) 3 polyunsaturated fatty acid docosahexaenoic acid (DHA) (91). The most prevalent omega-3 fatty acid in the brain is DHA. Data from animal models suggest that DHA may be a helpful treatment for AD due to its anti-amyloid, antioxidant, and neuroprotective qualitie (92).

8.3. Oestrogen

Despite epidemiological evidence to the contrary, there is no proof in clinical trials that oestrogens are effective in treating AD. In a research including 120 women with mild to severe AD, a year of estrogen replacement therapy did not slow the progression of the disease or improve global, cognitive, or functional outcomes (93).

8.4. Statins

Elevated cholesterol levels promote the synthesis of Ab, according to the cholesterol hypothesis, which is primarily supported by in vitro and animal studies (94). Furthermore, animals given "statins," or HMG-CoA reductase inhibitors, create less Ab. Although longitudinal epidemiological research has not shown a lower incidence of AD among statin users compared to non-users, retrospective studies have linked statin usage to a lower prevalence of Alzheimer's disease (95).

IX.Limitation of existing therapy

Single-target medications have been the mainstay of AD treatment techniques for many years, which is a significant drawback in the battle against this complicated condition. The paradigm shifted in favour of MTD discovery as a result of this restriction. Studies show that treatments that only target one target have not resulted in meaningful results, disease modification, or notable clinical benefits (96).

X.Conclusion

In conclusion, advances in pharmacological therapy are being made despite the fact that there is currently no cure for AD; new drugs with high efficacy, minimal side effects, and economic feasibility will surely be developed in the near future. Given the increasing prevalence of AD, a more advanced therapeutic approach is needed. Although some research clarifies the course of the disorder, there are currently few viable neuro-regenerative and neuroprotective treatments available. Advances in our understanding of the many targets associated with AD, such as intracellular and intercellular signal networks, have improved the disease's management. Improving drug delivery strategies and gaining important knowledge about the pathophysiology of illnesses must be the main goals of future AD research. At the same time, the study focused on the connections between several pathways, including neuroinflammation. Furthermore, even while the focus on creating new treatments is highly valued, we must remember that dementia is a complex, multidimensional condition that requires a multidisciplinary approach to care. In addition to drug therapy, our approach to managing dementia patients must remain thorough and well-rounded, emphasizing the complex biopsychosocial aspects of caring for this patient population.

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