1   Review

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3   **RECENT TREATMENT APPROACHES FOR ALZHEIMER'S DISEASE AND**

4   **POSSIBLE DRUG TARGETS**

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18 **Abstract**

19 Alzheimer's disease (AD) is currently a highly prevailing neurological disease that is

20 characterized by dementia. AD pathologically includes the formation of

21 neurofibrillary tangles leading to the accumulation of tau protein and deposition of

22 Amyloid ß (A ß) plaques that further contribute to neurodegeneration. Moreover,

23 reduced acetylcholine levels or increased metabolism by cholinesterase leads to

24 dementia and is currently an ongoing drug strategy. Antioxidants and use of

25 acetylcholinesterase (AchE) inhibitors is current management therapy for AD but

26 excessive use of AchE produces various side effects. Even though, there is a

27 significant increase in AD prevalence related to genetic factors. So, drug development

28 for AD is a big challenge and strikingly high failure rate. Therefore, AD is the most

29 prominent among all neurological disorders and contributes to the high patient burden

30 and also to health care, combating this problem is highly necessary. AD therapy can

31 be generally classified into three categories: regenerative, disease-modifying, and

32 symptomatic. The researchers have focused on amyloid theory, Tau theory,

33 neuroinflammation, oxidative stress, and many other pathways for the creation of

34 newer therapy. The concept of active and passive immunity has also been introduced

35 for AD therapy. The current article focuses on the pathological pathways involved in

36 AD along with the newer drug treatments and newer drugs under investigation for

37 AD.

38 **Keywords**: Alzheimer's Disease; Autoimmunity; Gut microbiota; Anti-amyloid

39 therapy; Antibody therapy

Introduction

Dementia is a syndrome, and about 60–70% of cases of dementia are Alzheimer's disease. Currently, more than 55 million people around the world suffer from dementia [1]. The prevalence of Alzheimer's disease among the population above 60 age group in China was found to be 3.20% [2]. The prevalence of Dementia in India among the 60-plus age group population is found to be 7.4% and 8.8 million people living with dementia [3]. An estimated 6.7 million Americans with an age group of 65 plus have Alzheimer's, which is 1 in 9, or 10.7% [4]. The common symptoms of the disease include lack of judgment, cognitive impairment, misplacing things, difficulties in doing daily tasks, confusion, and behavioral changes. [5]. The formation of neurofibrillary tangles of hyperphosphorylated tau and the accumulation of amyloid plaques in the brain are the pathological hallmarks of this neurodegenerative disease [6]. Different experimental studies revealed that in AD there is a loss of cholinergic neurons and a reduced level of acetylcholine, a well-known neurotransmitter for memory formation [7]. Acetylcholinesterase, an enzyme that is responsible for the breakdown of acetylcholine in the synaptic cleft in the case of AD the level of the enzyme increased [8]. The role of genetics in the progression of AD is well known, and there are different genes such as Presenilin 1, Presenilin 2, APP on chromosome 21, APOE4 gene, C9ORF72 gene, MAPT gene and GRN mutation that are responsible for AD [9, 10]. In the vicinity of these Aβ plaques, there was a rise in both GPAF expression and protein quantities, which also increased with tau accumulation. Although GPAF has not been studied as much as Aβ, tau and neurofilament light chain ultrasensitive immunoassays have produced encouraging results about GPAF's potential as a blood-based marker of AD. GPAF concentrations in plasma and serum are higher among individuals who fall in the clinical AD spectrum [11]. The study conducted by Vincent Planche et al. presents the initial findings on the biological and clinical significance of blood AD biomarkers in the MEMENTO cohort.

In their study, they found that when considering both cerebrospinal fluid and blood biomarkers, the concentrations of p181-tau, p217-tau, p231-tau and neurofilament light chain in both blood and CSF were equally effective in predicting the probability of developing Alzheimer's disease dementia over a period of 5 years [12]. This implies that during initial visits to memory clinics, when no other information about patients' health or sociodemographic status is available, blood and cerebrospinal fluid biomarkers such as p181-tau and neurofilament light chain can be used

interchangeably to categorise patients based on their likelihood of developing AD dementia within the next 5 years [13]. Within this framework, the moderate correlation observed between blood and CSF p181-tau does not indicate separate biological information but rather can be attributed to variations in preanalytical handling, differences in analytical performance between CSF and blood, the peripheral clearance of these peptides, and the patients' comorbidities [14, 15]. Amyloid precursor protein, total tau, and phosphorylated tau are the CSF-based biomarkers of the disease, and there are various animal studies that have reported an increase in these biomarkers in the AD model of rats [16]. When mass spectrometry techniques were used, CSF pTau217 showed larger differences between Alzheimer's disease and controls when compared to pTau181 [17]. The results of a sizable, multicentre cohort study demonstrated that plasma pTau217 can accurately distinguish Alzheimer's disease from non-Alzheimer's disease dementias in 96% of the cases, which is comparable to the performance of recognised CSF or tau-PET biomarkers [18, 19]. Additionally, tau-PET positive subjects were accurately diagnosed by plasma pTau217 [18]. Plasma pTau217 concentrations correlate with the density of cortical tau pathology in Alzheimer's disease but not in other tauopathies like FTD-tau, according to neuropathological assessments of cerebral tau-tangle pathology [20]. This finding highlights the specificity of plasma pTau for Alzheimer's disease tau pathology [21]. The study also demonstrated that plasma pTau217 increases roughly 20 years prior to the development of mild cognitive impairment in autosomal dominant Alzheimer's disease, which is consistent with findings demonstrating that plasma pTau217 becomes aberrant prior to tau-PET[22, 23].
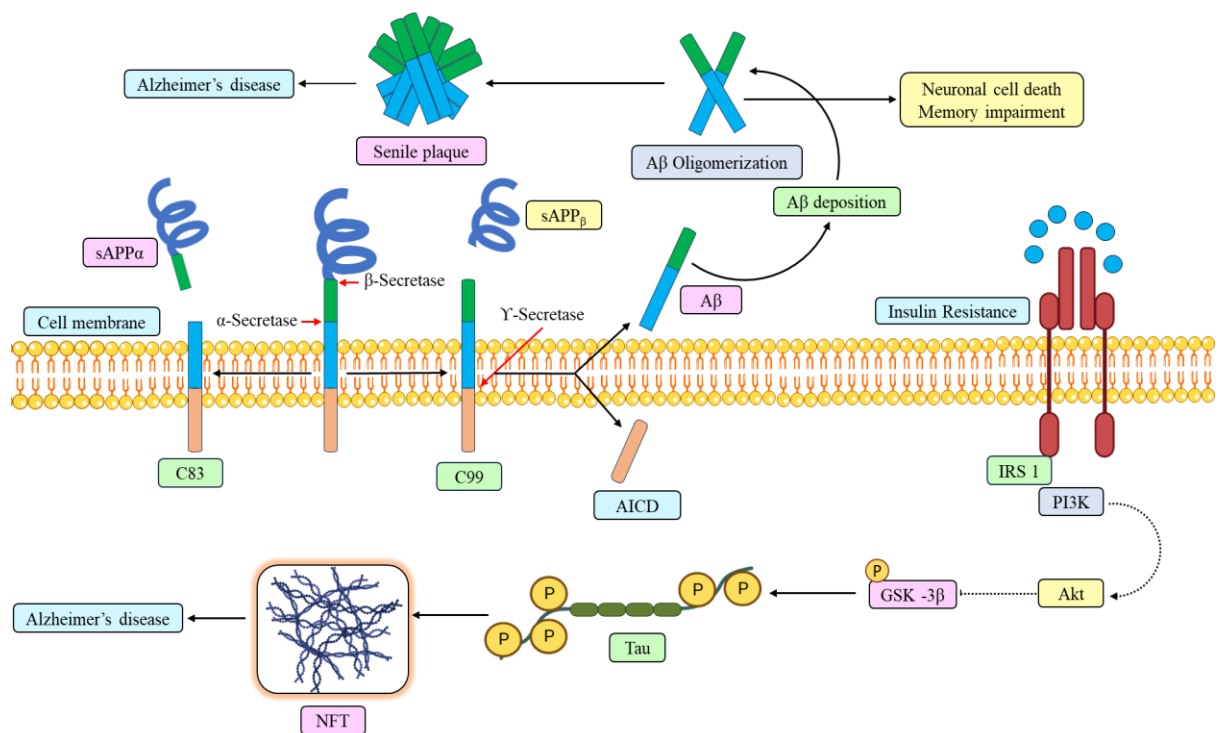
Pathogenesis of Alzheimer's Disease

Amyloid β hypothesis of Alzheimer's disease

Neuritic plaques, the pathological hallmark of the disease is a deposited peptide of 40 to 42 amino acids known as amyloid β [24]. Amyloid β is produced by the cleavage of the macromolecule amyloid precursor protein, the APP gene is located on chromosome 21 [25]. We can classify amyloid β as $A\beta_{1-40}$ and $A\beta_{1-42}$ [26]. $A\beta_{1-40}$ is good for neuronal survival and $A\beta_{1-42}$ that is deposited in AD patients is toxic for neuronal cells and leads to cognitive impairments. Basically, APP is processed by two pathways known as the amyloidogenic pathway, which is beneficial for neurons, and the non-amyloidogenic pathway, which is harmful for neuronal survival [27-29]. In

the non-amyloidogenic pathway, the enzyme α secretase that is responsible for cleavage of APP, cleaves its transmembrane fragment which is sAPPα, that has neuroprotective properties. sAPP$_\beta$ and 12-kd protein fragment C99 are produced by the amyloidogenic pathway by the action of β secretase. Enzyme ϒ secretase cleaves the carboxy terminal fragment into Aβ and AICD. Aβ deposited as a oligomers and forms neuritic plaques [30, 31]. The accumulation of Aβ oligomers results in the death of neurons. There are various animal studies that demonstrated that level of Aβ$_{1-42}$ increases the brain of animals [32, 33].

Figure 1: Process of Aβ formation and neurodegeneration in Alzheimer's disease.

Tau Hypothesis of Alzheimer's disease

One phosphoprotein that is phosphorylated is tau, which controls its ability to attach to microtubules [34]. Tau, a microtubule-associated protein, was among the first proteins studied by cell biologists [35]. It was given its name by Marc Kirschner, who was leading a team investigating elements that facilitate the formation of microtubules from tubulin [36]. Thus, tau is referred to as a tubulin-binding protein [37]. The human brain undergoes alternative splicing of the tau pre-mRNA, leading to the production of six distinct molecular isoforms of the protein [38]. The six tau isoforms

129   can be distinguished by the presence of either three (3R taus) or four (4R taus)

130   microtubule binding repeats (R) in the carboxy terminal half, each consisting of 31–

131   32 amino acids [39, 40]. Additionally, they can have one (1N), two (2N), or zero (0N)

132   amino terminal inserts, each consisting of 29 amino acids [41]. In 4R tau isoforms, the

133   extra repeat is the second repeat (R2) [42]. The process of alternative splicing of tau

134   pre-mRNA leads to the production of three 3R tau isoforms (0N3R, 1N3R, and 2N3R)

135   and three 4R tau isoforms (0N4R, 1N4R, and 2N4R). The 2N4R tau protein, also

136   known as tau441, is the longest variant of the tau protein found in the human brain,

137   consisting of a total of 441 amino acids [43]. The fatal human brain exclusively

138   expresses the lowest-size tau isoform, known as 0N3R tau352, which lacks both the

139   two amino terminal inserts and the additional microtubule binding repeat [44]. Tau

140   exhibits minimal secondary structure, primarily consisting of a random coil

141   conformation, with the presence of β structure observed in the second and third

142   microtubule binding repetitions [45]. The tau protein engages with tubulin and

143   promotes its assembly into microtubules while also enhancing their structural

144   integrity. Tau, akin to MAP1 and MAP2, is a phosphoprotein whose biological

145   activity is governed by the amount of its phosphorylation [46]. The physiological tau

146   protein in the brain contains an optimal ratio of 2–3 moles of phosphate per mole of

147   the protein [47]. This precise quantity is essential for the protein to efficiently attach

148   to tubulin and promote the assembly of microtubules [36]. The inclusion of an extra

149   iteration (repetition 2) in the 4R tau proteins, together with the inclusion of amino

150   terminal inserts (N1 and N2), both contribute to the heightened affinity of tau for

151   tubulin [48]. Consequently, the 2N4R tau (tau441) is comparatively more effective,

152   while the 0N3R tau (tau352, the fetal tau) is significantly less effective in promoting

153   microtubule assembly [49]. The six isoforms of tau are highly hydrophilic, which

154   means they have a great affinity for water [50]. As a result, they are soluble and can

155   withstand high temperatures without being affected. Tubulin is present in a typical

156   fully developed neuron in a quantity that exceeds that of tau by more than tenfold

157   [51]. Excessive production of tau in cultured cells can result in the creation of

158   aggregated microtubules [52]. Neurons from patients with Alzheimer's disease contain

159   hyperphosphorylated tau, which can be observed in two forms: helical/straight

160   filaments and soluble species [53]. Abnormally phosphorylated tau proteins from

161   Alzheimer's disease brains capture and remove normal tau, MAP1, and MAP2

162   proteins from the microtubules, causing the microtubules to break down in laboratory

163 conditions [54]. In patients with Alzheimer's disease, the microtubule system in
164 neurons affected by tangles is disturbed and substituted by PHFs [55]. Cellular health
165 greatly depends on the dynamics of microtubules, and tau plays a crucial role in
166 regulating these dynamics in both living organisms and laboratory settings within
167 neurons [56]. Abnormally phosphorylated tau protein from the brain of individuals
168 with Alzheimer's disease does not stimulate the formation of microtubules and instead
169 hinders the formation that is normally facilitated by tau and other microtubule-
170 associated proteins in laboratory settings and in cells that have been taken from the
171 body [57]. AD P-tau forms complexes with both normal tau and MAPs [58]. The
172 hyperphosphorylated tau possesses a characteristic that renders it an active agent in
173 the disruption of the microtubule system [59]. The study demonstrated that the
174 process of hyperphosphorylation of tau leads to its self-assembly into filaments [60].
175 Furthermore, this characteristic is no longer present after dephosphorylation [61].
176 However, filaments composed of hyperphosphorylated tau do not adhere to tau or
177 interfere with microtubules, indicating that the polymerized state of
178 hyperphosphorylated tau is inactive [62]. Comparable outcomes were reported when
179 employing a neurodegenerative model, Drosophila, that exhibited human tau
180 expression on motor neurons. Chouhan A.K. et al. demonstrated the toxicity of
181 soluble hyperphosphorylated tau by causing disruption to microtubules. [63].
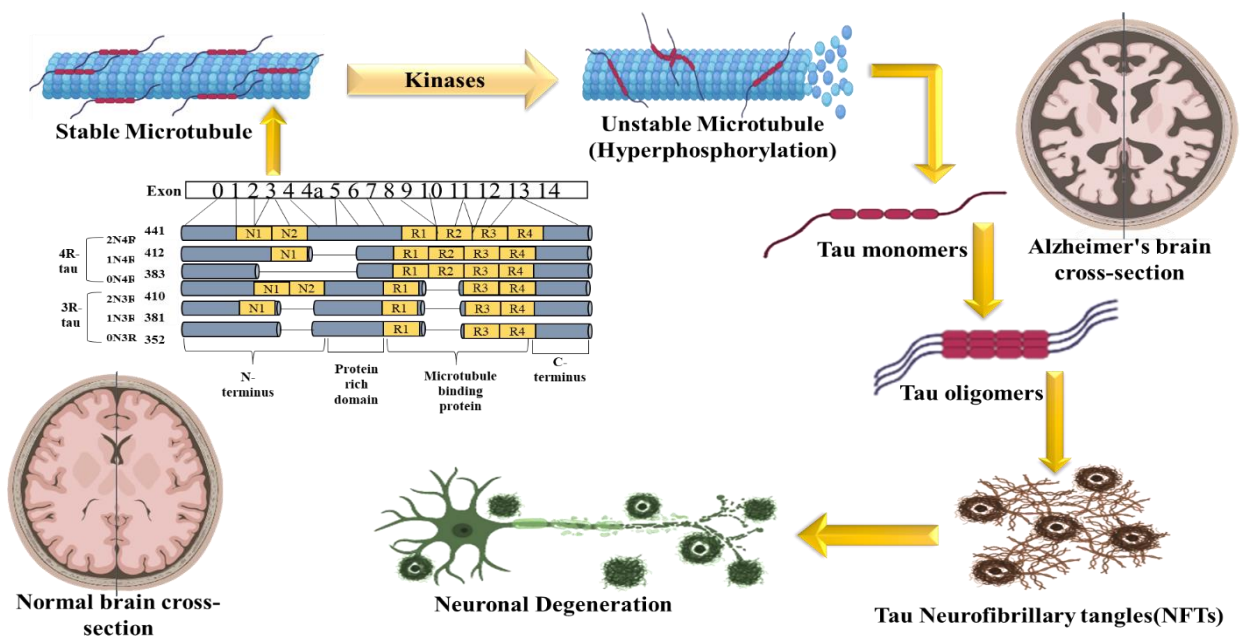

182 Figure 2: Microtubule formation and accumulation in the brain.

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AD as an Autoimmune Disease

This is a very new hypothesis of AD pathophysiology, which states that different pathogens and damage associated with immune-stimulating events such as depression, ischemia, and infection lead to the release and biosynthesis of Aβ as an initial immunopeptide and initiate an innate type of immunity cascade, and Aβ acts as an immunomodulator and shows antibacterial properties. The possible mechanism is that TREM 2, GAG, and NLRP3 receptors expressed on myeloid cells 2 and Aβ acting on these receptors increase the activation of microglia and the release of pro-inflammatory cytokines, resulting in neuronal apoptosis. Transmembrane potential gradients and anionic charge on macromolecules such as gangliosides in neurons that are present on outer leaflet have similar in neurons and bacteria leading to self-attack of Aβ on neurons [64-66]. This type of misdirected attack of Aβ on neurons of the brain results in formation of necrotic product of neuron that diffuse to the neighbouring cells and trigger more and more release of Aβ leading to self-initiated autoimmune reaction cascade. All these precipitates the clinical symptoms of AD such as memory impairments and problem in judgement. In this hypothesis of AD amino acids such as L-arginine and L-tryptophan metabolism appear as a regulator of innate immunity, and act as new therapeutic and diagnostic approach of AD. According to this hypothesis the serum level of these amino acids increases along with inflammatory markers [67].
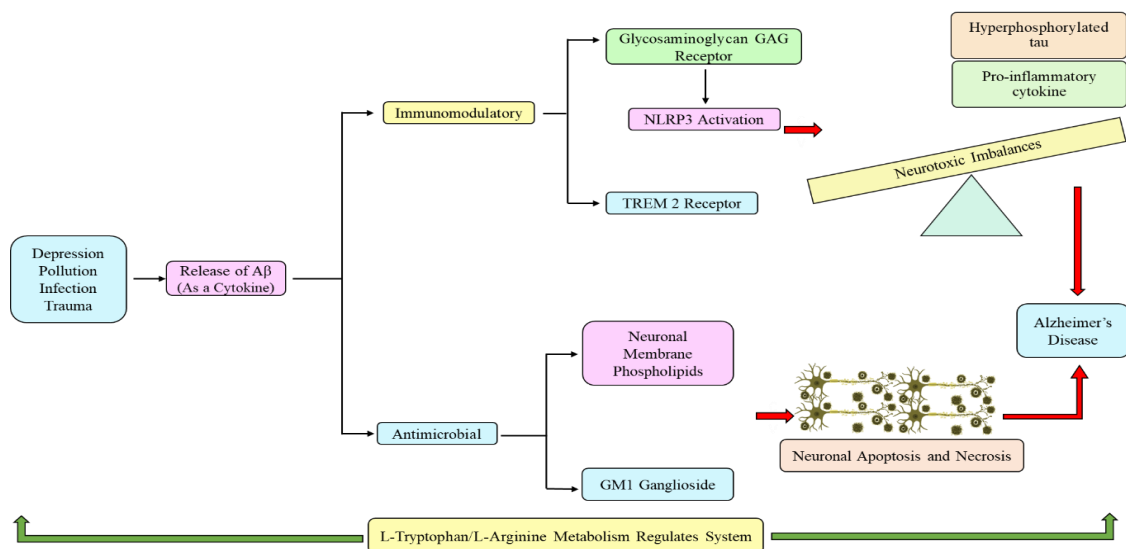
Figure 3: Various factors activates inflammatory response leading to apoptosis and Alzheimer's disease.
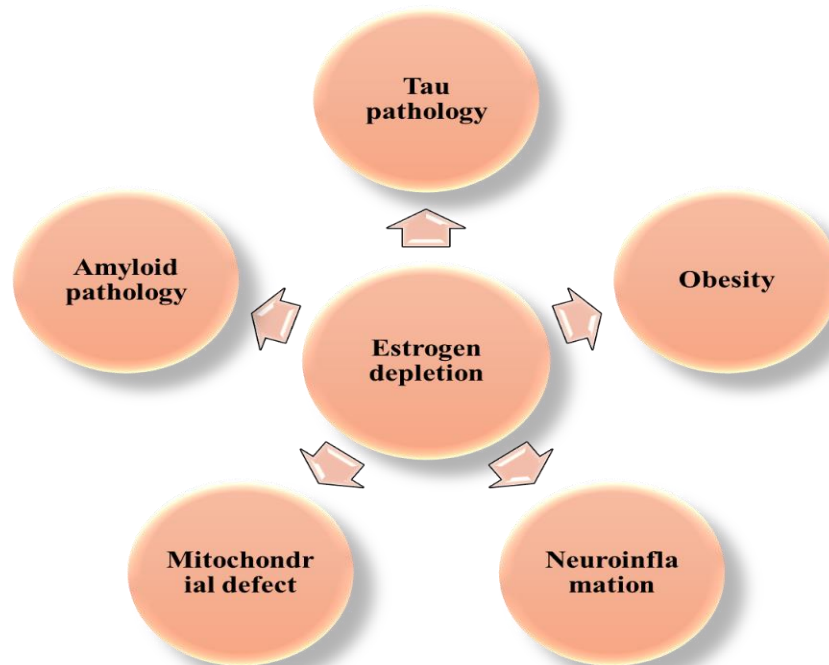
Vascular Hypothesis of Alzheimer's Disease

Vascular hypothesis of AD state that the abnormalities in cerebral vessels that leads to neurodegeneration and cerebral amyloid angiopathy and results in AD [68]. Changes in cerebral vessels and cortical blood flow initiates years to decades prior to the appearance of the symptoms of disease [69]. The cerebromicrovascular system has undergone a number of structural alterations, including thickening of the basal membrane, intimal atrophy, and a general decrease in intimal tight junctions. Functional cerebrovascular and substantial morphological malformations were seen in the brain of patients suffering from AD such as microvasculature malformations and atrophy, disruption of basement membrane and accumulation of proteoglycans, heparin sulfate, collagen IV and laminin, reduced density of the cerebrovascular network, alteration in endothelial cell which include rise in pinocytosis, the level of elevated endothelial cell markers such as E-selectin and VCAM-1 and levels of mitochondria were reduced [70, 71]. All these vascular alterations lead to micro-and macro-hemorrhages, ischemic lesions, and impaired cerebral blood flow [72]. The proteins responsible for inflammation are overexpressed in AD patients [73]. The cerebrovasculature abnormalities has a toxic effect on neurons; this mechanism is related to cerebrovascular changes and neuronal loss in AD [74]. Deposition of Aβ also contributes to the cerebrovasculature abnormalities and neuronal loss ultimately cause AD [73]. Metabolic dysfunctions such as hypometabolism of glucose in the brain is appeared decades before the progression of AD. Insulin easily crosses the BBB, and in the CNS, it exerts its action by binding to IR 1 and IR 2. Insulin regulates the two important pathways involved in the pathogenesis of AD. It regulates the PI3K/Akt pathway in the brain, and Akt inhibits the phosphorylation of GSK 3β, which is responsible for the abnormal phosphorylation of tau protein and the formation of neurofibrillary tangles. In cases of insulin resistance, Akt is unable to inhibit GSK-3β, which ultimately leads to AD. And Ras/ERK pathway which is major pathway involved in the cell growth, survival and gene expression.

Estrogen deficiency in perimenopausal female hypothesis of AD

Another hypothesis Specifically, the control of brain glucose metabolism by estrogen is disrupted during the perimenopausal period, leading to a condition of reduced metabolic activity [75]. Preclinical research suggests that during perimenopause, there is a decrease in brain estrogen levels, which leads to the breakdown of the systems

responsible for activating cerebral glucose metabolism rates and inhibiting the ketogenic pathways [76, 77]. After the decrease in cerebral glucose metabolism rates, there is a response called adaptive starvation that occurs to enhance the breakdown of fatty acids for the production and use of ketone bodies by mitochondria as a substitute source of energy [78]. The presence of hypometabolism, impaired mitochondrial activity, and resulting oxidative damage is recognised to contribute to the buildup of Aβ pathology and neuronal dysfunction, hence elevating the likelihood of developing Alzheimer's disease in the future [79]. These findings collectively offer more evidence that decreasing estrogen levels contribute to disrupted glucose metabolism in brain areas responsible for cognitive functions [80, 81].

Figure 4: Various factors activated cause estrogen depletion.

Role of gut microbiota in Alzheimer's diseases

The terminology "gut microbiota" refers to the symbiotic microbial human populations that inhabits the gastrointestinal system, consisting of bacteria, fungi, archaea, viruses, and protozoans [82]. Due to their significant involvement in controlling the body's balance and disease, they are increasingly recognized as crucial factors to the development of neurodegenerative disorders, such AD [83]. Contrary to previous beliefs, current findings have revealed that the gut microbiota plays a crucial role in facilitating communication between the intestine and the brain [84]. This two-

way interaction is referred to as the microbiota gut-brain axis [85]. Numerous physiological and pathological processes, including satiety, food intake, glucose and fat metabolism, insulin sensitivity, and stress, have been linked to this interaction between the central nervous system, autonomic nervous system, enteric nervous system, and the hypothalamus-pituitary-adrenal axis [86]. A novel approach to diagnosis and treatment for AD and other neurodegenerative illnesses may involve focusing on the microbiota, despite the fact that the processes behind this interaction remain poorly understood [87]. To our knowledge, there is currently a lack of a thorough understanding of gut microbiota-based diagnostic and therapeutic techniques, even though multiple published studies have explored potential microbiome-based therapeutics. We examine the potential for using microbiota-derived biomarkers for early disease detection here, drawing from the primary studies addressing gut microbiota dysregulation in AD [88]. A hypothesis has been proposed that suggests a connection between an imbalance in the gut microbiota and inflammation in the brain, which may lead to the development of Alzheimer's disease [89].

New Treatment for Alzheimer's disease

Drug development for Alzheimer's disease is a big challenge and strikingly high failure rate. Around two hundred forty-four medications were evaluated in AD clinical studies that were registered during the years 2002 and 2012, however out of these only one drug, Memantine is the only one to have completed clinical studies and received FDA approval; indicating only 0.4% success rate in the treatment of AD [90]. Being one of the most chronic neurodegenerative diseases, AD therapy can be generally classified into three categories: regenerative, disease-modifying, and symptomatic. The two approved treatments currently in use, glutamate antagonists and cholinesterase inhibitors are symptomatic and have some impact on cognitive function. Treatments for symptoms that more successfully target the cognitive domain and other distressing symptoms including psychosis, sleep disturbance, and agitation are still desperately needed in medicine [91]. The majority of present research attempts to discover novel treatments concentrate on altering the course of the disease. The idea for controlling this disease to be chronic includes preventing it from starting too soon or delaying its progression. Thus far, the majority of strategies have concentrated on tau biology and Aß cascade intervention. The third

approach for AD includes the control of regeneration, which however seems to challenge the therapy for AD [92].

Treatment targeting beta-amyloid:

Numerous anti-tau and anti-amyloid beta treatments have been studied or are being studied. Anti-amyloid treatments function by either decreasing the pathological β-amyloid oligomers, preventing the formation of β-amyloid plaques, or boosting the removal of β-amyloid peptides. However, a large number of anti-β-amyloid therapy trials have not shown a clinical benefit or raised safety issues.

Recent drugs considered targeting beta-amyloid:

Atabecestat

Atabecestat is presently undergoing phase 2/3 clinical trials to assess its safety and efficacy [93]. It is a drug with good BBB permeability based on the thiazine family. By preventing APP cleavage by the enzyme β-site amyloid precursor protein cleaving enzyme (BACE), it lowers the amount of Aβ in CSF or cerebrospinal fluid. The findings of a two-period extension study and a randomized, double-blind, placebo-controlled trial assessing the long-term safety and acceptability of atabecestat in early AD patients indicated that it was linked to the trend toward cognitive impairments.

Antibody treatment as anti-amyloid Therapy

a.   Aducanumab

Aducanumab was approved in the year 2021 as an anti-amyloid drug. With a high affinity, aducanumab, a completely human IgG1 monoclonal antibody, works by dissolving these β-amyloid clumps into smaller oligopeptides or amino acid. It has been demonstrated that aducanumab preferentially binds to parenchymal amyloid rather than vascular amyloid [94].

b.   Bapineuzumab

A humanized monoclonal antibody, bapineuzumab, has moved into phase 3 testing. It has shown effectiveness in enhancing cognitive function in patients with mild to moderate conditions [95].

c.   Solanezumab

Another anti-amyloid mAB that binds to soluble Aβ peptides is solanezumab. For mild AD carriers, the phase 3 clinical trials lasted 80 weeks. The research

demonstrated a noteworthy decrease in cognitive decline and loss of functionality. Additionally, biomarker findings in CSF indicated solanezumab's relationship with its target [96].

d.   Lecanemab

Lecanemab binds specifically to soluble Aβ protofibrils [97]. Its ability to dramatically slow down the progression of the disease by lowering the buildup of Aβ in the brain has been demonstrated in first clinical tests, suggesting that it may have disease-modifying capabilities. In a phase 3 interventional trial, Isai Inc. and Biogen® are investigating the anti-protofibrils antibody in people with early AD. The research will continue until 2024, To assess the therapeutic efficacy of this intervention in pre-clinical AD participants, phase 3 clinical research, has also been initiated in the US, Europe, and numerous other countries [98].

e.   Gantenerumab

An IgG monoclonal antibody called gantenerumab promotes Aβ plaque clearance by means of Fc receptor-mediated phagocytosis. Gantenerumab at 1,200 mg dose was shown to be able to stabilize Aβ plaque clearance in a PET substudy clinical trial. After gantenerumab was injected subcutaneously in big volume, no significant side effects were noted. This medication may drastically reverse the pathophysiology of amyloid plaques and change the course of the illness by halting or reducing the rate at which it progresses clinically [99].

f.   Donanemab

Phase III trials are presently being conducted on donanemab to treat early AD. Low baseline levels of full amyloid clearance were seen in 228 persons getting donanemab and 168 receiving a placebo in the four studies involving donanemab. Additionally, it was discovered that Tau buildup was slower [100].

Vaccines as anti-amyloid Therapy

a.   AN1792:

The first anti-Aβ vaccine (AN1792) showed that Aβ plaques could be successfully eradicated by active immunotherapy and that this effect could last for up to 14 years. However, in the Phase IIa clinical study, meningoencephalitis (ME) occurred in about 6% of AD patients receiving AN1792, which forced the trial's termination [101].

b.   ACC-001

ACC-001, a new vaccination, was created to prevent detrimental T-cell responses and speed up the clearance of Aβ plaques. Regardless of the use of the QS-21 adjuvant, Phase II clinical trials of ACC-001 in patients with mild and moderate AD showed that the vaccine had tolerable safety. Furthermore, it was discovered that ACC-001 + QS-21 generated greater anti-Aβ antibody titers compared to the QS-21-free control group [102].

c.   CAD106 & ABvac40

In another research of an AD preventive program, CAD106, an anti-Aβ vaccination containing peptide Aβ1-6, was discontinued due to aberrant changes in participant body weight, brain volume, and cognitive function. On the other hand, ABvac40, the first active vaccination that targets the C-terminal of Aβ40, has demonstrated good safety and tolerability in Phase I clinical trials [102].

Targeting Tau protein:

Since the creation of neurofibrillary tangles (NFTs) is a crucial marker of AD pathogenesis, tau protein targeting becomes essential for therapy regimens. Thus far, approaches have focused on tau immunotherapy in conjunction with tau deposition and phosphorylation. The two mechanisms responsible for increased neuron loss and the development of NFT are tau deposition and phosphorylation. It is possible to regulate the increased phosphorylation by blocking the glycogen synthase kinase 3 (GSK3) enzyme. However, Lithium being the GSK3 inhibitor, failed to show positive results in clinical trials [103].

Drugs targeting tau protein

a.   Blarcamesine

Tetrahydro N, N-dimethyl-2,2-diphenyl-3-furanmethanamine hydrochloride is the chemical formula for Blarcamesine, an experimental medication under research for AD. It decreases tau hyperphosphorylation, additionally, it is known to attenuate oxidative stress, and neurodegeneration in AD by targeting protein misfolding and acting as a muscarinic receptor agonist and sigma-1 receptor activator. Its antioxidant and anti-apoptotic properties have been demonstrated. It is currently in stage 2/3 of clinical trials [104].

b.   Thiamet G

It is a potential O-GlcNAcase (OGA) enzyme inhibitor, however, in the tau transgenic model TG4510 it has shown to decrease tau phosphorylation. It's in phase 1 clinical testing right now [105].

c.   Telmisartan

It is hypothesized that it reduces CSF tau and plaque formation in the brain, safeguards the cerebral microvasculature, and regulates cerebral blood flow. It is currently in Phase 2 clinical trials [106].

Vaccines as anti-tau Therapy

a.   AADvac1 Vaccine

Clinical trials are presently being conducted on a vaccine called AADvac1. It works by encouraging the production of antibodies that target tau's conformational epitope areas, which lowers tau deposition. Since the generated antibodies could recognize tau proteins in patients with mild to moderate AD, the human vaccination proved to be more effective than the animal experimentation method. Phase 2 trials for the vaccine are presently underway [107].

b.   ACI-35

ACI-35 reduced soluble and insoluble Tau in models of tau-transgenic mice. Currently, ACI-35 has successfully entered phase 2 clinical trials [108].

Antibody treatment targeting tau protein:

Semorinemab

Preclinical research in mice models showed that semorinemab targeted maximal binding across several extracellular Tau species. The first phase of investigations on semorinemab is over. Two ongoing Phase II trials have just concluded; one trial involved individuals with probable or prodromal AD, while the other had those with intermediate AD. Improvement was observed in the clinical features of AD patients in both trials [109].

Gosuranemab

Gosuranemab is a humanized mouse monoclonal antibody that targets extracellular Tau by recognizing a phosphorylated epitope in the N-terminal region of Tau that is composed of amino acid residues 15AGTYGLGDRK24. In Phase 1 trials, gosuranemab was proven to be safe and well-tolerated. It also showed that the amount of unbound N-terminal Tau in CSF had decreased. Unfortunately, Gosuranemab did

not lower AD biomarkers such as total Tau and ptau181. Gosuranemab is now undergoing a Phase II clinical trial, which is expected to be finished in 2024 [110].

Zagotenemab

Zagotenemab is another humanized antibody that targets the tau protein. Phase I clinical trials have been completed. Zagotenemab has shown positive outcomes in phase II clinical trials by attenuating the clinical manifestations of patients with early AD [110].

GLP-1 analogue

Intestinal epithelial endocrine L cells produce GLP-1, a 30-amino acid peptide hormone. GLP-1 increases the release of insulin from pancreatic cells and decreases insulin resistance. There are various studies conducted on the experimental animals suggest that GLP-1 analogues show neuroprotective effect in AD. Peng X et al. demonstrated that Exendin-4, a GLP-1 analogue, has a neuroprotective effect in diabetic mice with cognitive impairment by increasing the synthesis of insulin [90]. Gad SN et al. showed that lixisenatide has a protective effect on hippocampal CA1 neurons in experimental rats and can be used as a treatment for AD [91]. Semeglutide, liraglutide and dulaglutide, another analogue of GLP-1, also possess neuroprotective effects in the AD model of experimental animals. And the possible mechanism of action is modulation of hyperphosphorylation of phosphor protein tau by GSK 3β [92-95]. Femminella GD et al. conducted a phase II randomized controlled trial in participants with very mild cognitive impairment. After 12 months of the study, outcomes suggest that there is a decrease in microglia activation in a subgroup and a decreased level of tau and amyloid beta in a subgroup [96].

Drug treatment targeting neuroinflammation in AD

Neuroinflammation is one of the main causes of the progression of Alzheimer's disease. NSAIDS such as indomethacin have anti-inflammatory properties and are utilized as a treatment strategy for AD. Karkhah A et al. demonstrated that indomethacin reduces neuroinflammation in the STZ-induced Alzheimer's disease model of experimental animals. The results of the study showed that indomethacin decreased CARD, NLRC4, NLRP3, and IL-1β and improved learning and memory performance [97]. VX-745, Selective p38 MAP Kinase Inhibitor is in the phase II of the clinical trials. Researchers working on VX-745 because it inhibits p38 MAP

16

kinase that is responsible for the release of proinflammatory cytokines and activation

464 of microglia [98].

465

466 **Recent Treatment strategy targeting gut microbiota**

467 In vitro, the fermented milk produced by Lactobacillus helveticus IDCC3801 caused a

468 drop in the quantity of amyloid precursor protein-β [99]. Furthermore, it significantly

469 reduced the level of β-amyloid in a rat model. Probiotic ethanolic precipitate

470 treatment significantly reduced the mice's scopolamine-induced amnesia [100]. The

471 findings revealed that amyloid precursor protein metabolism may be used by L.

472 helveticus IDCC3801-mediated fermented milk to ameliorate AD-associated memory

473 impairments [99]. In mouse models of accelerated aging-related memory deficits, the

474 probiotic intervention alleviated the condition. To be more precise, giving L. pentosus

475 var. plantarum C29 to C 7BL/6J mice improved the memory impairment caused by D-

476 galactose. In mice treated with D-galactose, injections of 1×10^{10} CFU of C29

477 restored the expressions of cAMP response element-binding protein, hippocampus

478 doublecortin, brain derived neurotrophic factor (BDNF), arginase I and II, TNF-α, IL-

479 10, and CD206. In addition, the injection of C29 effectively reduced the expression

480 of inflammatory markers (iNOS, COX-2, p-FOXO3a, and p-p65) and senescence

481 marker (p16) in mice treated with D-galactose. In the D-galactose-induced aged mice

482 experiment, the results showed that the injection of C29 reduces the memory

483 impairments and M1 macrophage-polarized inflammation. Similarly, giving L.

484 plantarum MTCC1325 (12×10^8 CFU/ml; 10 ml/kg body weight) to albino rats

485 treated with D-galactose for sixty days reduced the rodents' AD symptoms [101]. The

486 administration of MTCC1325 to rats effectively restored normal cognitive function,

487 histological structure (including amyloid plaques and tangles), and acetylcholine

488 levels that were disrupted by D-galactose. According to the findings, MTCC1325

489 might have anti-Alzheimer's properties [102]. The behavioral and memory function

490 abnormalities in AD-induced ddY mice were assessed by Kobayashi et al. after

491 administering 1×10^9 CFU of B. breve A1. B. breve A1 supplementation improved

492 the altered behavior and memory deterioration and decreased the production of

493 immune-reactive genes and hippocampus inflammation-associated genes, according

494 to the Journal Pre-proof Journal Pre-proof data. B. breve A1 may help mice with Aβ-

495 induced cognitive impairment [103]. After administering a probiotic cocktail

496 supplemented with 2×10^{10} CFU of B. longum, B. breve, B. infantis, L. acidophilus,

L. paracasei, L. plantarum, L. brevis, and L. delbrueckii subsp [104]. Bulgaricus (SLAB51), the oxidative stress in AD mice was went down. Significant improvements in SOD activity, recovery of carbonyls and 4-hydroxy-2-nonenal levels, and redox enzyme activity are all brought about by SLAB51 treatment. SLAB51 treatment reversed the dysfunction in the mediators of DNA repair and oxidation in AD mice. The study findings conclusively showed that SLAB51 has the ability to enhance the effects of aging and oxidative stress associated with Alzheimer's disease through the Sirtuin-1 pathway [105]. The administration of a synbiotic preparation, which includes L. plantarum NCIMB 8826, L. fermentum NCIMB 5221, B. longum spp. infantis NCIMB 702255 (3 $\times$ 109 CFU), and 0.5% Triphala (Emblica officinalis, Terminalia chebula, and T. bellirica) powder, decreased the probability of AD development in Drosophila melanogaster [106]. Through metabolic, oxidative, and immunological signalling pathways, the synbiotic supplementation mostly improved the gut-brain axis [107]. The synbiotic treatment resulted in an increase in the survival rate and a decrease in Aβ deposition in the flies [108]. The study proposed that synbiotics are a powerful treatment agent for delaying the onset of AD [109]. In summary, the outcomes of experiments conducted on live animals indicate that the addition of probiotics improves the physical, psychological, and cognitive health problems associated with Alzheimer's disease by regulating gene expression and responding to oxidative stress.

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