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Neuropathological Mechanisms of Alzheimer's Disease: Complications and Potential Treatments

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ABSTRACT

Alzheimer's Disease (AD) is a neurodegenerative disorder that targets the brain and disrupts vital processes of neural networks causing the decline of cognitive function. The main pathological mechanisms responsible for the development of Alzheimer's are the tau and amyloid-beta proteins. These proteins are detrimental because they form plaque and neurofibrillary tangles that aggregate within the brain. Biomarkers and diagnostic tools are utilized to detect Alzheimer's within a patient. These devices can potentially detect the onset of Alzheimer's early, reducing the severity of symptoms. Throughout studies of various research articles, certain potential AD treatments were analyzed to determine their efficacy. Galantamine was found to be a potent inhibitor of acetylcholinesterase and more effective than rivastigmine and donepezil. A controversial herbal supplement, *Ginkgo Biloba*, was examined to determine its relevance in reducing the severity of Alzheimer's. Research findings support that the supplement's efficacy is inconclusive as trials have not been able to provide significant evidence as to whether or not *Ginkgo Biloba* is effective in the case of Alzheimer's. By investigating the impact of prospective treatments on the mechanisms of Alzheimer's, this extensive research aims to provide evidence to handle the effects of the disease and determine significant treatments to ensure the quality of healthcare for all patients distressed by Alzheimer's Disease.

Introduction

The most prevalent cause of dementia is Alzheimer's Disease. According to the World Health Organization (2023), Alzheimer's accounts for 60-70% of all dementia cases worldwide. The disease was named after a German doctor: Dr. Alois Alzheimer. In 1906, Dr. Alzheimer discovered microscopic changes such as distinctive plaques and neurofibrillary tangles in the brain autopsy of a 50-year-old woman. These factors contributed to memory disturbance, paranoia, aggression, and later her death. This widespread disease has many complications and mechanisms that progressively diminish cognitive function, primarily in the brain. This disease starts with the formation of tau and beta-amyloid proteins. The deposits of tau proteins form tangles in brain cells. Subsequently, beta-amyloid proteins deposit plaque around the brain cells. These detrimental proteins deteriorate neuron receptors and cause apoptosis within the hippocampus and entorhinal cortex (starting sites of Alzheimer's). This abruption causes loss of memory and drastically reduces spontaneous thinking abilities.

Fortunately, several non-invasive diagnostic devices can detect Alzheimer's Disease: magnetic resonance imaging (MRI), computed tomography scans (CT), and positron emission tomography (PET). There are certain risk factors and biomarkers that are indicative of Alzheimer's Disease. Age, genetic history, and hypertension are some of the many risk factors for the disease. Analyzing cerebrospinal fluid or measuring tau and beta-amyloid 42 proteins are essential biomarkers for diagnosing Alzheimer's**.** These biomarkers reveal invaluable insight into the development process of the disease. Even though there are many ways to detect Alzheimer's, no evidence of a potential cure has been found. Some approved treatments that reduce the mild to moderate symptoms of Alzheimer's are galantamine, rivastigmine, and donepezil. An herbal remedy, ginkgo biloba, is a rising controversial treatment for reducing the severity of Alzheimer's Disease. Researchers have run many trials on the efficacy of ginkgo biloba, but the primary

outcome has been inconclusive**.** However, cutting-edge technology and prospective treatments can likely reduce the severity of the neuropathological mechanisms of Alzheimer's Disease. Conducting this study is extremely vital to understanding and mitigating the development process of Alzheimer's.

Risk Factors and Biomarker Evaluations of Alzheimer's Disease

There are many risk factors and biomarkers necessary to assess before diagnosing Alzheimer's. Biomarkers are essentially used to monitor the development of a disease. They specifically measure biological indicators within the human body. In the case of Alzheimer's, the most common biomarker is cerebrospinal fluid (CSF). Risk factors are characteristics that precede susceptible conditions.

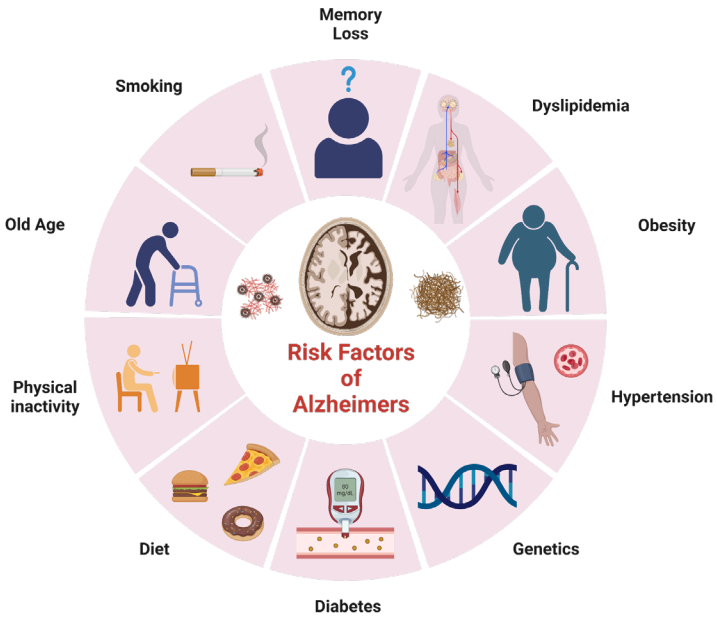

Figure 1. Diagram displaying risk factors associated with Alzheimer's. Adapted from "Risk Factors of Dementia", by BioRender.com (2023).

Risk factors associated with AD are age, genetics, hypertension, diabetes, low education levels, low levels of physical activity, etc. Exercise modulates amyloid-beta turnover and shows improvements in cerebral blood flow. To be physically active, older adults should perform moderate-intensity aerobics for at least 30 minutes, 5 days/week to maintain a healthy lifestyle. A systematic review of 16 studies with more than 160,000 AD patients found a 45% reduction in the risk of developing Alzheimer's due to the regular 20-30 minutes of physical activity five days a week. Hence, physical activity plays a crucial role in preventing or reducing the rigor of Alzheimer's.

Aside from physical activity, gender is also considered a risk factor for AD. Approximately two-thirds of AD patients are women (Rosa et al., 2020). This is due to the prominent longevity of women over men. In America, the average woman lives to 81, five years longer than the average man. Throughout the last century, women have had fewer opportunities for higher education than men. However, over the last few decades, there has been a decline in the percentage of Alzheimer's for women as there has been a significant improvement in education attainment. Statistically, women exercise more frequently but less intensively than men, resulting in a higher risk of Alzheimer's as physical activity is a key risk factor (Nomaguchi & Bianchi, 2004). There are many risks involved in Alzheimer's but involuntary characteristics like gender can influence the development of AD.

There are several widely investigated biomarkers for the molecular and degenerative process of Alzheimer's that can be supportive of the diagnosis. Cerebrospinal fluid (CSF) is a clear liquid that encompasses the brain and spinal cord which provides security and layers of insulation. Physicians conduct lumbar punctures to collect CSF. This is examined by injecting a hollow needle between two lumbar bones (vertebrae) to withdraw CSF samples. The CSF measures protein activity such as amyloid 42, tau, and phosphorylated tau which are all pathological mechanisms of Alzheimer's Disease. Hence, cerebrospinal fluid is the primary biomarker for measuring the fluctuation of protein levels and aiding in interpreting Alzheimer's.

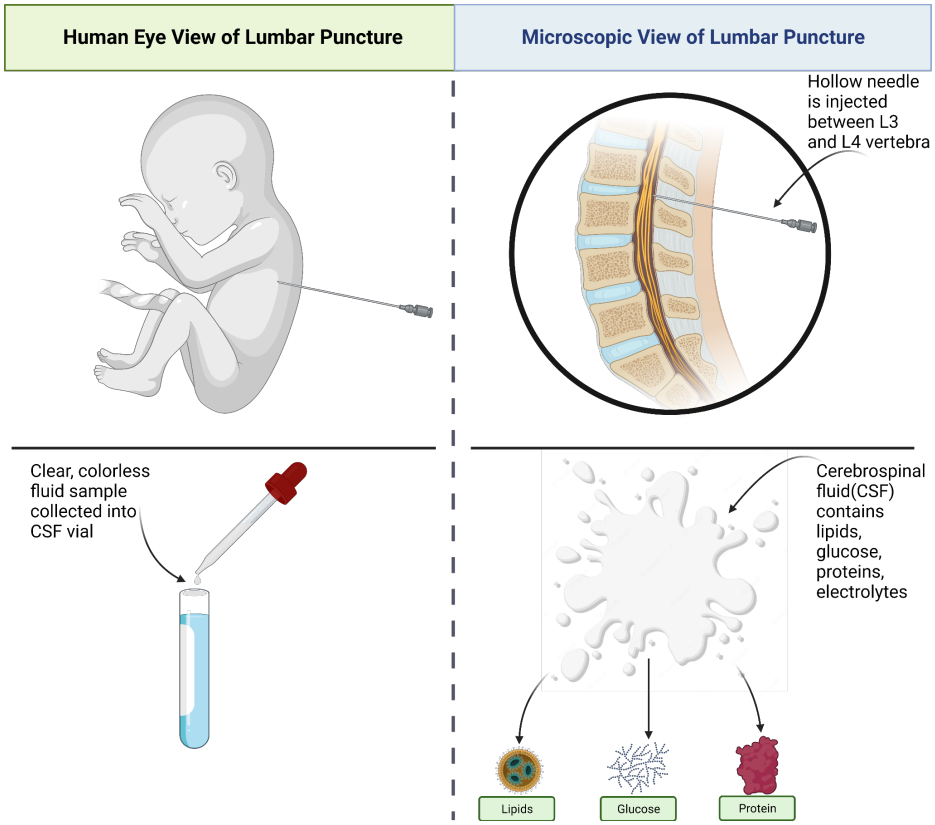

Figure 2. Diagram indicating lumbar puncture process.

There are other critical biomarkers that need to be taken into consideration to indicate Alzheimer's. Genetic tests analyze deoxyribonucleic acid (DNA) from blood or oral samples like saliva to determine the genetic makeup. Blood tests can also measure proteins in the brain, specifically Aβ proteins during Alzheimer's studies. They are most commonly used in research facilities to investigate early detections and potential treatments. These biomarkers are considerable but generally have less accuracy than CSF when identifying Alzheimer's.

Advancements in technology have enhanced biomarker findings. Before the early 2000s, Alzheimer's could only be discovered through brain autopsy report. Currently, researchers can identify Alzheimer-related changes in the brains of alive patients with Alzheimer's. In addition, scientists can track the onset and progression of the disease. Researchers are continuing to learn and develop biomarkers to make exceptional strides in preventing Alzheimer's and finding potential treatments. The advancements and evaluations of biomarkers are indispensable for diagnosing early or preventing patients from developing Alzheimer's.

Current Diagnostic Techniques of Alzheimer's Disease

Specific screening devices have improved the rate and accuracy of diagnosing Alzheimer's. These are the effective diagnostic tools to diagnose Alzheimer's: magnetic resonance imaging (MRI), computed tomography scans(CT), and positron emission tomography (PET). There are specific requisites needed for the optimal usage of these diagnostic devices. "The two hallmark pathologies required for a diagnosis of Alzheimer's disease (AD) are the extracellular plaque deposits of the β-amyloid peptide (Aβ) and the flame-shaped neurofibrillary tangles of the microtubule-binding protein tau" (Murphy & Levine, 2010). Many research articles have claimed that the tau (neurofibrillary) tangles and Aβ peptides (derived from amyloid beta precursor protein) are the main pathological findings necessary for diagnosing AD. Every diagnostic tool specializes in certain anatomical aspects to detect Alzheimer's. Depending on the type of scan, certain image segmentations of gray matter loss and other findings are highlighted in the hippocampus and entorhinal cortex. Ultimately, each scan quantifies multiple diverse aspects of Alzheimer's pathology and evaluates the comparisons and rational changes over time.

Although discoveries in scans are essential for the development of Alzheimer's, the timing of detection is equally important in the process. Detecting Alzheimer's early is essential for the well-being of a patient. Fortunately, this is available due to the advancements in brain imaging techniques. "The early and accurate detection of Alzheimer's disease-associated symptoms and underlying disease pathology by clinicians is fundamental for the screening, diagnosis, and subsequent management of Alzheimer's disease patients" (Porsteinsson et al., 2021). Past research papers have also shown conclusive findings regarding the importance of detecting the disease early. Specifically, early detections enable patients to seek interventional treatments quickly. This provides more time for the physicians to prescribe potential therapies to ameliorate the symptoms of Alzheimer's. These rapid measures are of immense importance for patients to plan for the future and achieve a better quality of life.

Magnetic resonance imaging (MRI) is a non-invasive medical tool that uses magnetic fields and radio waves to produce detailed images of anatomical structures. The time frame of a typical MRI test is about 15-90 minutes. Specifically in Alzheimer's, MRIs show structures in the brain that have been atrophied. Volumetric MRI scans categorize AD as progressive cerebral atrophy. Voxel-based morphometry (VBM) is an MRI technique that is highly effective in detecting differences in specific anatomical figures resulting in the diagnosis of AD. VBM specifically depicts gray and white matter volume within the human brain. Research studies have shown that patients with Alzheimer's consistently exhibit gray matter volume reductions within the hippocampus and other subregions. Reductions of white matter loss were predominantly found in the temporal lobe and inferior longitudinal fasciculus. VBM approaches in MRI technology show patterns of gray and white matter reductions that flaunt the mechanisms of Alzheimer's.

A computed tomography scan (CT) is a diagnostic imaging tool that utilizes computerized X-ray technology to manifest images of brain structures. Similar to MRIs, CT scans can detect structural changes within the temporal lobe and hippocampus to support the diagnosis of Alzheimer's. Criteria for a CT diagnosis of Alzheimer's: enlargement of cortical sulci and increased ventricle sizes. The scan can also show brain atrophies, blood vessel changes, and buildup of fluids. Cerebrospinal fluid leaks are a major biomarker for AD and can also be detected within a CT scan. CT scans are accurate and efficient when it comes to the diagnosis process of Alzheimer's.

CT scans can potentially increase the risk of cancer. X-rays within CT scans produce ionizing radiation. Ionizing radiation interacts within cells and deposits large amounts of energy into areas that can disrupt chemical bonds and cause biological effects in living tissues. Although CT scans can seem detrimental to cells, there is a low risk of developing harmful conditions from X-ray radiation exposure.

Positron emission tomography (PET) utilizes radioactive material to produce three-dimensional images of the internal body. PET scans take approximately 60 minutes. It requires a small amount of radioactive glucose to be injected into the vein. This injected radioactive material helps evaluate and determine the active areas within the brain. Specifically in Alzheimer's, Pittsburgh Compound B is used in PET scans to image beta-amyloid plaques in brain cells. "Positron emission tomography (PET) studies of cerebral metabolism with fluoro-deoxy-d-glucose (FDG) and

amyloid tracers such as Pittsburgh Compound-B (PiB) have shown characteristic changes in the brains of patients with AD" (Johnson et al., 2012). Research has proven that PET scans show impairment of cerebral metabolism within the posterior cortex – indicating signs of Alzheimer's. Using different radioactive compounds, PET scans can be a reliable tool to find beta-amyloid plaques, further aiding in the diagnosis of Alzheimer's.

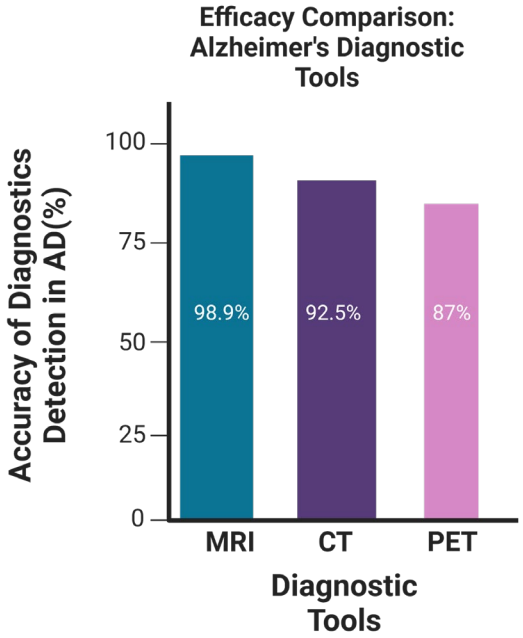

Figure 3: Graph approximating the efficacy of different diagnostic imaging tools. Information from "Influence of MRI on Diagnostic Efficacy and Satisfaction of Patients with Alzheimer's Disease" (Dong et al., 2021). "The Appropriate Use of Neuroimaging in the Diagnostic Work-Up of Dementia" (Bermingham, 2014).

Diagnostic tools are vital in the detection process of Alzheimer's. The data from the bar graph depicts the efficacy of each Alzheimer's diagnostic device. MRIs had the highest detection accuracy succeeding CT scans by 6.4%. MRI data was found from previous studies and experiments, the control group had 42 healthy people and the test case had 66 patients with Alzheimer's. To stress the efficacy of MRI, the differences in structural brain changes between the AD patients and the healthy control group had to be analyzed. Compared to the control group, the left and right hippocampal volumes of AD patients were significantly smaller. Different studies suggested percentages of effectiveness: 99.10% and 98.60%. Averaging out to 98.90% as an estimated MRI effectiveness rate. Although magnetic resonance imaging could be regarded as the most effective diagnostic device, many other critical factors need to be evaluated before settling on a specific scan.

Overview of Alzheimer's Mechanisms

The amyloid-beta peptide (Aβ) plays a major role in the pathogenesis of Alzheimer's disease. The Aβ peptide deposits plaque around the hippocampus and entorhinal cortex. Later, the plaque accumulates and marches through other regions of the brain. The aggregation of amyloid plaques induces synaptic dysfunction, neural connectivity disruptions, leakage of ions, and additional miscellaneous actions. Many view Amyloid-β as the neurodegenerative cause of Alzheimer's

Amyloid beta proteins are formed when amyloid precursor proteins(APP) break down. APP is sequentially broken by two proteolytic enzymes, β-secretase and γ-secretase. β-secretase (BACE1) activity cleaves through APP

to release sAPPβ and produce CTF99. Subsequently, the γ-secretase cleavage of CTF99 results in the formation of Aβ peptides. Particularly in Alzheimer's, the β- and γ- secretase generate Aβ species that substantially form within the brain and contribute to further amyloid-beta aggregations. Contributions from two transmembrane proteases capable of cleaving amyloid precursor proteins have influenced the behavior of the detrimental mechanism – Aβ peptides.

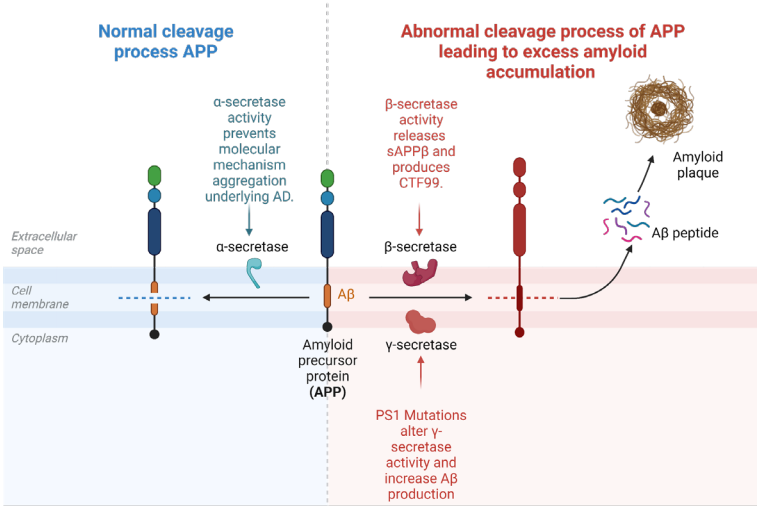

Figure 4. Diagram resembling normal and abnormal cleavage processes of the amyloid precursor protein with labeled protease. Adapted from "Cleavage of Amyloid Precursor Protein (APP)", by BioRender.com (2023).

Amyloid β proteins have many pathological influences upon them. The role of aromatic side chains is of heavy importance when it comes to the aggregation of Aβ proteins. Amyloid-beta proteins have opposing sides of hydrophilic and hydrophobic amino acids. It contains a "charged N-terminus, a central hydrophobic region, LVFFA (Aβ (17–21)), and a long hydrophobic C-terminal tail" (Cukalevski et al.,2012). The central hydrophobic region is a major element in the aggregation process. The central hydrophobic section contains two phenylalanine residues. Phenylalanine is a hydrophobic, aromatic amino acid. When self-assembled with toxic fibrils, (forming phenylalanine-fibrils) it can initiate an amyloid aggregation procedure. Studies have shown two aromatic rings of the phenylalanine compound, Phe19, and Phe20, significantly affect the aggregation rate. Leucine substituted phenylalanine within the Phe19 and Phe 20 because of its hydrophobic similarities and lower tendencies of the beta-sheet which enabled the usage of "ThT assays" to thoroughly study the "aggregation kinetics" within the amyloid fibrils. In addition, findings have reported that Thioflavin (ThT) correlates strongly with aromatic and leucine residue. The investigation concluded that "position 19 contributes to accelerating the aggregation process" but in contrast, the "aromatic side chain in position 20 retards it." (Cukalevski et al.,2012). As a result, the involvement of certain compounds in aromatic chains has negatively impacted and fastened the aggregation process of Amyloid β proteins.

The aggregation of proteins is an important aspect involved in the appearance of Alzheimer's, but another issue of AD occurs within the accumulation of misfolding proteins. Optimal hydrogen bonding structures are critical for the prevention of protein mishaps. "The main force driving the correct folding mechanism is the hydrophobic effect" and in such cases "when this folding kinetics is altered". Another crucial element is conducted "by water molecules and by their ability to form a complex network of hydrogen bonds whose dynamics influence the mobility of protein amino acids" (Mallamace et al., 2018). Proteins of complex chains of amino acids can be considered polypeptides. Interestingly, the amino acids' specific interactions within each other form peptide structures such as alpha-helices and beta-sheets. Beta sheets form the fibrils and protein aggregates involved in AD development. The structure of proteins, alpha-helices, and beta-sheets are built up by hydrogen bonds and hydrophilic interactions. Thereby stressing the influence of hydrogen bonds in the folding and structural process for proteins.

Experiments from past research papers have brought awareness to the microscopic insights and hydrogen bonding efficacy in the folding/unfolding proteins processes. Previously, the researchers developed kinetic models for the "nucleation mechanism of protein folding (NMPF) and barrierless protein denaturation (BPD) by using the mean first passage time analysis" (Djikaev & Ruckenstein, 2010). However, hydrogen bonding effects produced incorrect results lowering the hydrogen bonding accuracy. To improve the results of the experiment, probabilistic hydrogen bond (PHB) models were developed to exhibit the effect of hydrogen bonding networks around two solute particles. This model accurately read the results of the solute particles and determined that hydrogen bond networks play a crucial role in the protein folding/unfolding process.

Another pathophysiological finding that is tremendously important when it comes to the development process of Alzheimer's is tau proteins. Tau undergoes certain changes and procedures that formulate the aggregation process. Normally, tau proteins' role is to stabilize microtubules which are essential for the transportation of axons. In pathophysiological terms, tau becomes hyperphosphorylated, experiencing various changes and causing microtubules to disassemble. Research papers suggest that "tau hyperphosphorylation results from perturbation of cellular signaling, mainly through an imbalance in the activities of different protein kinases and phosphatases" (Medeiros et al.,2010). This catastrophic action causes tau to construct tau oligomers freely. The further aggregation of tau oligomers initiates the formation of neurofibrillary tangles. Neurofibrillary tangles consist of certain plaques and phosphorylated tau. Neurofibrillary tangles are hallmarks of Alzheimer's which can form and aggregate inside brain cells. These series of actions signify the critical relationship between tau proteins and other sub-components that initiate neurofibrillary aggregation.

Autophagy ("self-eating" in Greek) is the process of cell breakdown which destroys abnormal proteins in the cytoplasm. In scientific terms, autophagy is the "conserved pathway for the degeneration of aggregated proteins" (Hamano et al., 2018). In Alzheimer's, autophagy is disrupted and causes toxic proteins like tau and Aβ to aggregate. "Tau accumulation disrupts autophagosome-lysosome fusion by disrupting ESCRT-III complex formation" (Feng et al., 2020). ESCRT-III's (Endosomal sorting complexes required for transport) leakiness can cause tau to escape from the endolysosomal department and promote tau aggregation. Tau proteins are vicious elements that intensively disturb autophagy, ultimately influencing aggregation.

Contrary to the aggregation process, tau degeneration is essential for the amelioration of Alzheimer's. As discussed before, autophagy is a known process for the deterioration of tau proteins. Research studies have shown that tau proteins are completely degraded by the ubiquitin-proteasome system and the autophagy-lysosome pathways. In contrast to the human brain, an interesting experiment explored the role of the proteasome in rat neurons rather than questioning tau degradation. Surprisingly, tau amounts were found to decrease when proteasomal inhibitors were utilized. Physiologically, proteasome and autophagy systems can prevent the accumulation of tau and likely prevent an Alzheimer's outburst.

Unsurprisingly, amyloid and tau proteins are the two most common neuropathological mechanisms involved in Alzheimer's disease. The Aβ proteins form the amyloid plaques, and the neurofibrillary tangles are composed of the hyperphosphorylated tau proteins. These destructive proteins are configured in the hippocampus and entorhinal cortex. Neurofibrillary tangles (NFTs) are known to entwine in the brain cells and cause further harm. NFTs block axonal transport, causing apoptosis (cell death) and neuronal dysfunction in neurons. Concurrently, the abnormal level of amyloid forms plaque around the neurons. This process can also cause cellular dysfunction and synaptic loss. Amyloidosis and hyperphosphorylation are two processes that can result in the aggregation of amyloid and tau proteins, respectively. As shown, tau and Aβ proteins are the driving forces of the pathogenesis of Alzheimer's. The tau and amyloid pathology is immense and is still being deeply discovered.

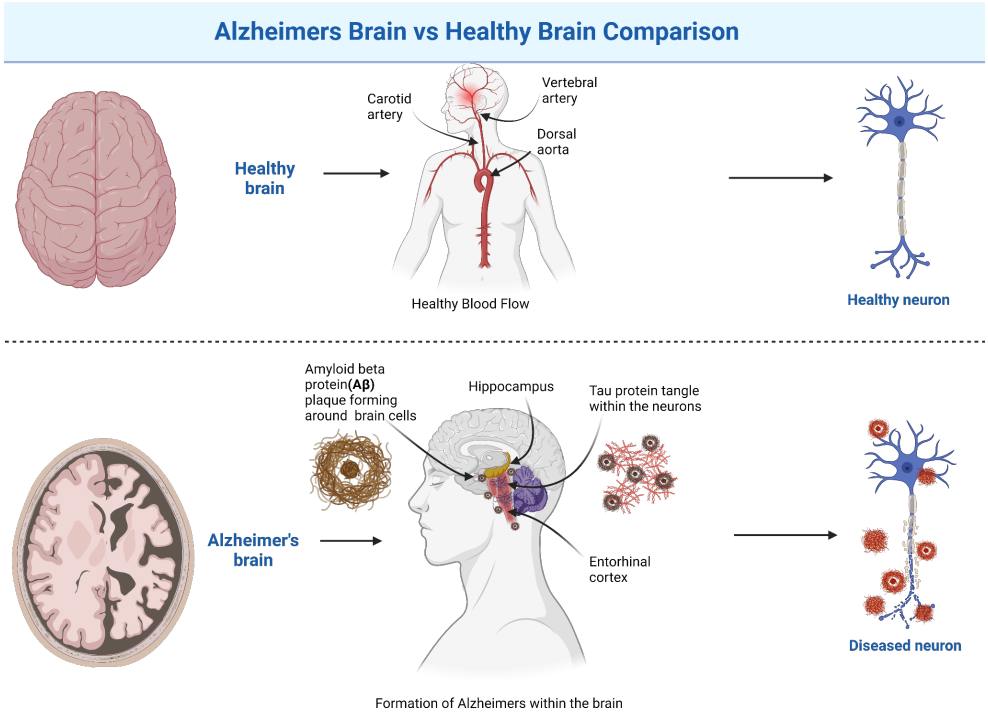

Figure 5: Diagram comparison of healthy brain and Alzheimer's brain atrophy with labeled pathological mechanisms.

Potential Treatments to Reduce the Ferocity of AD

To this day, many trials are being run to figure out potential treatments to reduce the severity of Alzheimer's. Galantamine, rivastigmine, and donepezil are three cholinesterase inhibitors that could alleviate the symptoms of Alzheimer's. Acetylcholinesterase (AChE) is an enzyme that mainly terminates neurotransmitters and contributes to synaptic loss. It can cause severe sweating, seizures, and eventually death. AChE may also function to promote amyloid-beta proteins by increasing the deposition of peptides causing amyloid plaques to accumulate. Thus, the three discussed cholinesterase inhibitors function to prevent the breakdown of acetylcholine reducing the rapid onset risk of Alzheimer's Disease. An herbal supplement, ginkgo biloba, has been a controversial topic and studies have been made to discover the effectiveness of this treatment. For many years, the efficacy of ginkgo biloba has been inconclusive resulting in an unclear status as to whether ginkgo biloba is a significant treatment in the case of Alzheimer's. Potential treatments are essential to minimize and alleviate the symptoms of Alzheimer's and any other fatal diseases.

Galantamine is a significant acetylcholinesterase inhibitor that is used as a medication for Alzheimer's. Galantamine is a heterocyclic phenantridine compound, derived from the *Galanthus woronowii* flower. Galantamine binds to nicotinic acetylcholine receptors (nAChRs) which apply "positive cholinergic effects mediated by indirectly increasing activity at nicotinic acetylcholine receptors"(Hoskin et al., 2019). nAChRs are mediators of anti-inflammatory pathways and they deactivate oxidative stress. Studies have concluded that nAChRs activation may be a potential target for Alzheimer's treatments because the pathological mechanisms, neuroinflammation, and oxidative stress, can be reduced within the binding role of galantamine and nAChRs. In 2001, galantamine was approved by the Food and Drug Administration (FDA). Galantamine is only taken orally. 4mg tablets and 8mg capsules taken twice a day is the most common dosage to further boost cognitive functions. Galantamine is a highly effective drug recommended for alleviating mild to moderate symptoms of AD.

Rivastigmine is another oral cholinesterase inhibitor that is used to treat neurodegenerative diseases like Alzheimer's. In 1985, Mary Weinstock-Rosin discovered rivastigmine. Throughout the years, rivastigmine has been approved in 60 countries including the United States of America. Rivastigmine hinders both acetylcholinesterase and butyrylcholinesterase by covalently binding to active sites on these enzymes. Rivastigmine blocks those enzymes that inactivate neurotransmitters in the synaptic cleft. Studies reveal that rivastigmine patients taking 6-12 mg per day orally or 9.5 mg per day by skin patches show statistically significant results in cognitive and behavioral functions (Cochrane Library, 2015). However, the drug can cause adverse side effects such as nausea, vomiting, diarrhea, or weight loss. In addition, rivastigmine can be associated with minimal serum enzyme elevations and apparent liver injuries. Rivastigmine is a potential treatment that is advised for mild to moderate symptoms of AD, but there are adverse side effects that can occur during therapy.

Donepezil is the third common oral acetylcholinesterase inhibitor that is used as a treatment for Alzheimer's. Donepezil is a piperidine derivative that "binds reversibly to acetylcholinesterase and inhibits the hydrolysis of acetylcholine" (Kumar et al., 2015). The mechanism action of donepezil is similar to rivastigmine. However, donepezil has fewer adverse side effects and is evident to perform significantly better on measures of memory and cognitive function compared to rivastigmine. The drug has been approved by the FDA for the treatment of mild, moderate, and severe Alzheimer's. For mild to moderate AD, the initial dose is 5 mg per day. Moderate to severe AD can steadily increase to 23 mg per day. Donepezil is a successful and reliable treatment option for any stage of Alzheimer's.

Ginkgo biloba is a highly investigated herbal supplement that conceivably treats cognitive and neurodegenerative disorders. *Ginkgo biloba* is currently the oldest living tree species worldwide. The place of origin is believed to be in the valleys of eastern China. *Ginkgo biloba*, derived from dried leaves of Ginkgo, is a controversial topic of discussion when it comes to the efficacy of treating Alzheimer's. Some studies report that Ginkgo ameliorates cognitive function in elderly AD patients, while others find *Ginkgo biloba* to be an unreliable treatment for Alzheimer's. This ongoing discussion brings Ginkgo to hold inconclusive results in reducing the severity of AD.

The *Ginkgo biloba* extract (GBE) has many mechanisms and components that make up the herbal treatment. Bilobalide, Ginkgolides A-C, Quercetin, Hydroxykinurenic, Kaempferol, Glucose, Rhamnose, and Isorhamnetin are the active components in the *Ginkgo biloba* extract. These active components found in GBE "improve blood circulation, reinforce the walls of the capillaries, discourage clot formation, and protect nerve cells from harm when devoid of oxygen. The leaf extracts are used to treat dementia disorders, such as concentration difficulties and memory impairment" (Singh et al., 2019). Studies have reported that GBE restricts the production of amyloid beta in the brain by lowering free cholesterol, as Aβ is supposed to be affected by free circulation and intracellular cholesterol levels. However, we know the efficacy of Ginkgo in Alzheimer's is still to be specified.

Conclusion

Alzheimer's has historically been a devastating disease that has impacted mankind with many obstacles. As pathological mechanisms were investigated, global research efforts contributed to discovering many biomarkers and prospective treatments to ameliorate the adverse effects of Alzheimer's. Potential treatments including *Ginkgo biloba* and Galantamine were heavily investigated throughout this paper. Research studies concluded that galantamine was highly effective, while *Ginkgo Biloba* had inconclusive results on the efficacy of treating Alzheimer's. Research articles illustrated in this paper stress the importance of early detection of AD to reduce the aggregation process of the two major hallmarks, tau and amyloid proteins. 21st-century technology has provided access to diagnostic tools and measures to prevent Alzheimer's. Research advancements would not have been possible without the thousands of people who have graciously volunteered in clinical trials and experimental studies. In conclusion, optimistic findings and rising technology have expedited Alzheimer's therapy which can significantly affect the growth of future generations.

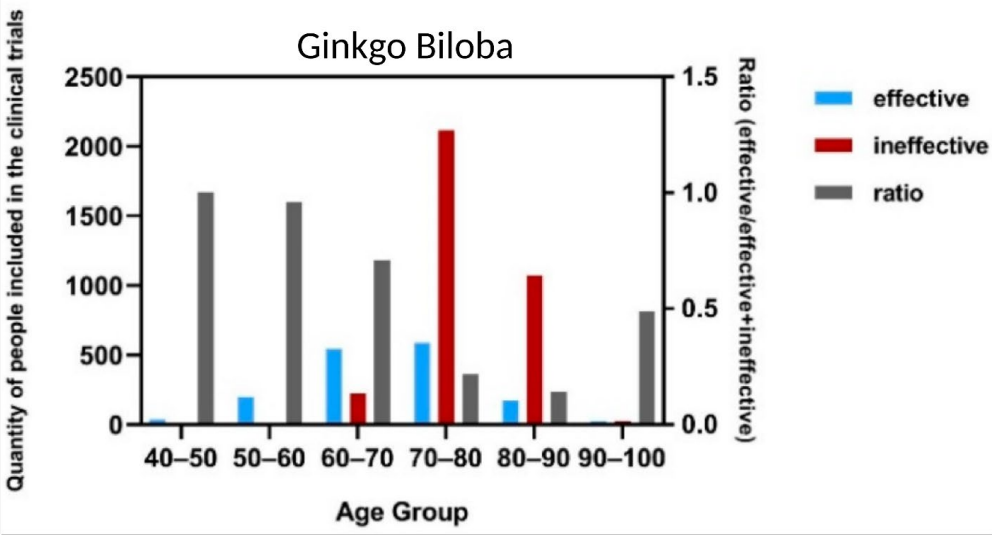

Figure 6. Graph exhibiting the efficacy of Ginkgo biloba in reducing the severity of Alzheimer's. Adapted from "Can We Use Ginkgo Biloba Extract to Treat Alzheimer's Disease? Lessons from Preclinical and Clinical Studies" (Xie et al., 2022).

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