Journal of Carcinogenesis
Covering Genesis to Therapeutics

Journal of Carcinogenesis, ISSN: 1477-3163
2025; Vol 24: Issue 7s, https://carcinogenesis.com/

Revolutionizing Alzheimer's Disease Treatment: The Role of Novel Drug Delivery Systems and Artificial Intelligence

Tolepbergenova M.[1], Rupanshi Sahu[2], Lidiya Khituova[3], Zholdasbay Altay Danaiuly[4], Abdugani Musayev[5], Alexandr Leonov[6], Abdukhalil Musaev[7], Sanjay Nagdev[8], Zhannat Nurmakhanova[*9]

[1]Department of Pathological Physiology; Kazakh National Medical University named after S.D. Asfendiyarov

[2]PhD Scholar, Sagar Institute of Research Technology-Pharmacy, Sanjeev Agrawal Global EEeducation University, Bhopal, India

[3]Department of Pediatrics with a course of children's Infections diseases, Kazakh-Russian Medical University, Almaty, Kazakhstan

[4]Intervention cardiologist, Almaty Multiprofile Clinical Hospital

[5]Department of Emergency and First Aid, Asfendiyarov Kazakh National Medical University, Almaty, Kazakhstan

[6]Department of Molecular biology, general chemistry and biochemistry with the course of medical genetics Kazakh-Russian Medical University, Almaty, Kazakhstan

[7]Department of congenital and acquired ENT diseases, Republican Specialized Scientific and Practical Medical Center of Pediatrics, Tashkent, Uzbekistan

[8]Dept. of QA, Shri Prakashchand Jain College of Pharmacy & Research Jamner India

[*9] Associate Professor, Dept. of General Medicine Asfendiyarov Kazakh National Medical University, Almaty, Kazakhstan

***Corresponding author**

Zhannat Nurmakhanova

Email ID: zhanna12932@mail.ru

ABSTRACT

Alzheimer's disease is a multifaceted neurodegenerative disorder with no definitive cure, posing significant challenges in treatment. Recent advancements in drug delivery systems, particularly through nanotechnology, and the integration of artificial intelligence and machine learning, have offered promising new avenues for enhancing AD management. Nanoparticle-based drug delivery systems are being utilized to improve the targeting and bioavailability of therapeutic agents, allowing more efficient crossing of the blood-brain barrier. Concurrently, AI-driven approaches are being employed to facilitate early diagnosis, optimize treatment strategies, and predict patient outcomes by analyzing complex datasets, including brain imaging and biomarker data. Also, a multidrug, multi-target treatment approach, similar to chemotherapy, is emerging as a potential strategy for addressing the complexity of AD. This review discusses the various AI and nanotechnology-driven innovations in AD, the current challenges in treatment, and the future directions for research. Continued exploration of these technologies, combined with early detection, lifestyle interventions, and precision medicine, holds the potential to revolutionize AD care, minimizing disease recurrence and enhancing patient quality of life.

Keywords: *Alzheimer's disease, drug delivery systems, nanotechnology, artificial intelligence, machine learning, blood-brain barrier*

How to Cite: Tolepbergenova M., Rupanshi Sahu, Lidiya Khituova, Zholdasbay Altay Danaiuly, Abdugani Musayev, Alexandr Leonov, Abdukhalil Musaev, Sanjay Nagdev, Zhannat Nurmakhanova, (2025) Revolutionizing Alzheimer's Disease Treatment: The Role of Novel Drug Delivery Systems and Artificial Intelligence, *Journal of Carcinogenesis*, *Vol.24, No.7s*, 414-431

1. INTRODUCTION

Alois Alzheimer first characterized Alzheimer's disease (AD) over a century ago as "senile dementia," that causes gradual decline in mental and physical health, ultimately leading to death [1]. The World Alzheimer's Report 2019 indicates that around 6.7 million Americans are currently affected by AD, with projections suggesting an increase to 14 million by 2050 in the United States [2]. In 2019, the projected price of treatments was 340 billion USD, with projections suggesting it may escalate to 1.1 trillion USD by 2050. The Australian Institute of Health and Welfare (AIHW) stated that approximately 472,000 individuals in Australia are affected by Alzheimer's, with projections indicating an increase to 589,000 by 2028 [3]. AD-related dementia is among major cause of death in the country, with a 2018–2019 fiscal year cost of $3 billion. The cost is expected to treble by 2058, with 849,300 dementia cases and 533,800 women [4]. Alzheimer's accounts for 70% of dementia cases nationwide. The estimated yearly cost of dementia, including all expenses is $15 billion [3]. Demographic and financial patterns show how important AD is for medical professionals and systems globally.

FDA-approved AD medicines fall into two categories. Cholinesterase inhibitors (ChEIs) prevent acetylcholine breakdown early in the disease. Combining NMDA receptor blockers and AChE inhibitors in advanced stages can slow disease progression [5, 6]. These pharmacological groups are usually available in tablets and capsules. Clinical and preclinical studies demonstrate that these drugs significantly alleviate disease burden and enhance cognitive function. Their ability to slow disease progression by integrating them into sophisticated drug delivery systems tailored for brain targeting. To improve CNS disease treatment efficacy, specialised drug delivery devices are needed [7]. Due to their capacity to eliminate Aβ plaques and aggregates, aducanumab and lecanemab received fast FDA approval [8, 9]. Yet, their impact on disease development is still debated [10].

Existing pharmacological interventions for AD do not effectively impede or reduce the neurodegenerative progression. These interventions offer symptomatic relief, focusing mainly on cognitive symptoms, yet they are linked to significant adverse effects. Rivastigmine, galantamine, donepezil, and tacrine are acetylcholinesterase inhibitors that are part of the therapy plan, along with memantine, an NMDA receptor antagonist [11]. More research on the causes of AD is needed since current treatments are ineffective. Although multiple hypotheses have been suggested, none adequately account for this intricate disorder [12]. The most recognized hypotheses include amyloid-beta, tau, cholinergic, and oxidative stress, accompanying secondary pathologies including glutamate excitotoxicity and inflammation. A variety of drug candidates exhibiting different pharmacological actions have been investigated [13].

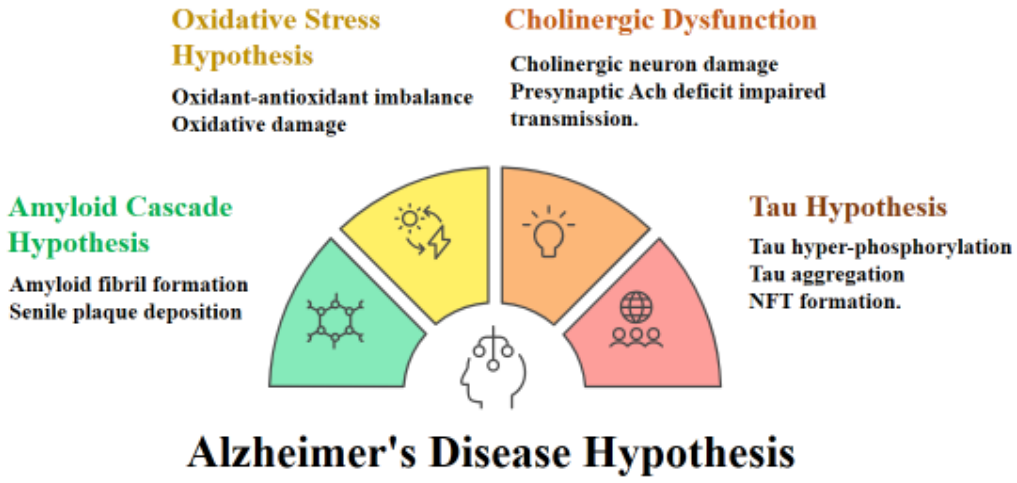

Fig.1: A concise overview of the predominant underlying theories of AD

2. PATHOPHYSIOLOGY OF AD

Despite considerable progress in clarifying biochemical, and cell processes in AD, the underlying etiology and pathogenesis remain unclear, impeding the advancement of effective disease-modifying therapies [14]. Pathological characteristics of AD include amyloid-beta (Aβ) plaque accumulation, neurofibrillary tangles and catastrophic neuronal loss. The etiology of AD is influenced by a genetic predisposition; however, recent evidence links this condition to gliosis, inflammation,

mitochondrial dysfunction, generation of reactive oxygen species (ROS) and a significant accumulation of metal ions (see Fig. 2) [15, 16, 17]. The following sections examine these critical pathological pathways and examine prospective pharmaceutical targets for AD treatment.

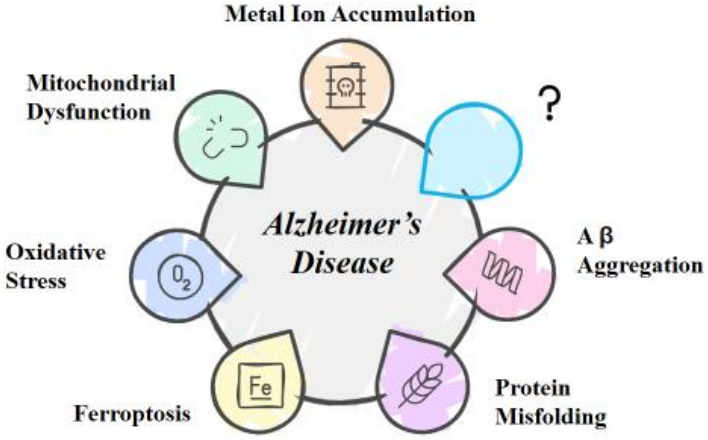

Fig. 2. Main AD pathophysiological pathways

2.1 Amyloid-β (Aβ) cascade

According to the amyloid-β cascade principle, Aβ, a proteolytic component of APP cutting, is crucial for the formation of AD. APP, a type I membrane protein discovered in neuron somatodendritic and axonal sections, has one across domain, a large exposed area, and a short cytoplasmic tail [18, 19]. Non-amyloidogenic and amyloidogenic APP degradation pathways are shown in Fig. 3. APP is initially broken down by α- or β-secretases at the external domain, leading to accessible ectodomains and membrane-bound C-terminal segment. In both processes, γ-secretase cleaves C-terminal sections in the transmembrane region, resulting in similar cytosolic peptides called the APP intracellular domain [20, 21].

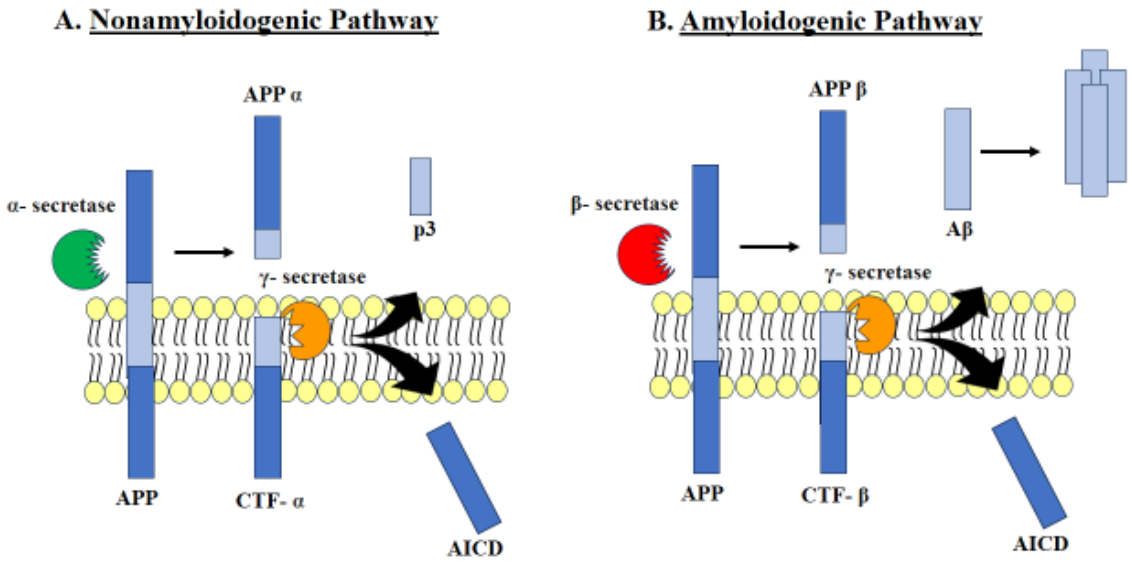

Fig.3: AD is characterized by two pathways: nonamyloidogenic (A) and amyloidogenic. (A) The non-amyloidogenic route uses α-secretase to cut APPα into its soluble ectodomain and the C-terminal fragment α (CTF-α). γ-secretase cleaves the CTF-α, resulting in the non-amyloidogenic fragment p3. (B) β-secretase (BACE-1) makes the soluble ectodomain APP and the C-terminal fragment ² during the amyloidogenic process. CTF-β cleavage by γ-secretase produces Aβ peptides, which combine to form disease-specific amyloid plaques. In both processes, γ-secretase produces similar cytosolic polypeptides called APP intracellular domains (AICD).

In the non-amyloidogenic pathway, -secretase initially cleaves APP, which is subsequently managed by -secretase. Separation by α-secretase generates the soluble ectodomain APPα and the C-terminal fragment α. γ-secretase cleaves the C-terminal fragment α, yielding p3, a non-amyloidogenic peptide devoid of clinical significance (Fig. 3). The amyloidogenic route entails BACE-1 (β-secretase) followed by γ-secretase processing. The breakdown of APP by β-secretase leads to the breakdown of the soluble ectodomain of APP and the C-terminal fragment. γ-secretase cleaves the C-terminal segment β at several locations, resulting in the production of Aβ peptides (Fig. 3) [18], [19], and [20]. Aβ peptides cause neurotoxicity because of their self-aggregation. Aβ monomers can group together and make protofibrils and fibrils, which can lead to oxidative stress, problems with mitochondria, changes in membrane permeability, inflammation, problems with synapses, and excitotoxicity [22].

2.2 Tau hyperphosphorylation

The second most important histological feature is neurofibrillary tangles. Tau, a microtubule-associated protein family phosphoprotein, is found in axons, somatodendritic areas, and glial cells [23]. Tau helps convey axons and preserve dendritic structure by stabilizing and assembling microtubules. Phosphorylation at many sites regulates its biological function. Tau's affinity for microtubules decreases with abnormal phosphorylation, making it more aggregable. This hyperphosphorylation impairs microtubule assembly, disrupts axonal transport and dendritic structure, and leads to synapse loss, neuronal death, and eventually, dementia [24].

Multiple variables cause Tau-mediated toxicity, involving calcium imbalance and oxidative damage. However, two key mechanisms are primarily linked to Tau's abnormal hyperphosphorylation in AD. First, Tau undergoes conformational changes in AD-affected brains, rendering phosphorylation a greater probability than dephosphorylation. PP1 and PP2A dephosphorylation mechanisms typically restore Tau to its regular condition [24]. It experiences phosphorylation at over 30 serine/threonine debris in AD, notably by glycogen synthase kinase-3 (GSK-3) and calcium/calmodulin-dependent kinase-II (CaMKII) [25, 26]. Among these, the GSK-3β isoform is particularly important in promoting Tau hyperphosphorylation, establishing it as a crucial treatment goal for impeding or postponing disease progression [27, 28].

2. 3 Oxidative Stress

Oxidative stress (OS) results from a disparity in the synthesis and removal of oxidants, stemming from inadequate antioxidant mechanisms of defense, which causes a buildup of free radicals. The oxidative alteration of lipids, proteins, and nucleic acids arises mainly from this imbalance [29, 30]. Reactive species from endogenous sources and exogenous stimuli, are essential for multiple biological processes, including receptor-mediated signals and the control of apoptosis [27].

OS can lead to disease progression and worsen symptoms directly and indirectly. Reactive species can directly damage and kill cells. H2O2, functioning as a secondary messenger, may interfere with redox signals and influence biological reactions through protein alterations, mitochondrial dysfunction, and by initiating inflammation and apoptosis. OS in AD is linked with neurodegeneration via four primary factors: i) Development and accumulation of Aβ, ii) stimulation of microglia, iii) irregularities of redox-active metal ions, and iv) abnormalities of mitochondria [31].

OS has been demonstrated to contribute to the enhanced formation of senile plaques by reducing α-secretase efficiency while simultaneously increasing both β- and γ-secretase efficiency [32, 33]. Additionally, the accumulation of oligomers further promotes oxidative stress, as Aβ has been found to elicit a concentration-related rise in ROS levels and to enhance their generation through the direct activation of NADPH oxidase [34, 35, 36]. Postmortem studies of AD brains have shown a significant build-up of OS markers, including protein and nucleic acid damage, along with impaired antioxidant defenses and the deposition of redox-active metals. In AD, redox proteomics investigations have found oxidative injury to energy metabolism enzymes and proteasome components [37, 38, 39, 40].

The accumulation of Aβ and hyperphosphorylated Tau leads to the stimulation of glial cells in the CNS, serving as a histopathological marker of the disease, with neuroinflammation observed in areas impacted by AD. Although chronic neuroinflammation is often seen as a neuroprotective response, it can lead to neurotoxicity and neurodegeneration [34]. Microglia work as the localized immune cells of the CNS, functioning as the primary protection against stimuli that promote inflammation and playing a vital part in tissue preservation. When Aβ accumulates, microglia become stimulated to combat the toxic effects. Yet the inflammatory mediators released by activated microglia are accountable for neuronal harm in AD [41, 42, 43, 44]. In AD, microglia that had produce ROS and proinflammatory cytokines leading to inflammation [44]. Activated microglia release inflammatory mediators that can cause reaction astrocytosis, leading to a secondary reaction. Astrocytes engage with neurons, offering support via neurotransmitter maintenance and facilitation of the development of synapse [45]. In AD, reactive astrocytes contribute significantly to neuroinflammation and produce free radicals, which can worsen neuropathology and neurodegeneration. Although reactive astrocytes have been noted for their role in clearing Aβ plaques, their effectiveness diminishes once plaque clearance capacity is overwhelmed or morphological changes occur, leading to increased Aβ pathology due to Aβ release from astrocytes [46, 47, 48]. Consequently, astrocytes are emerging as potential therapeutic targets for neurodegenerative diseases, as reviewed elsewhere [49, 50, 51, 52]. Reactive astrocytes

and oxidative stress-activated microglia may cause synaptic loss, aggravate Tau pathology by raising kinases involved for Tau hyperphosphorylation, facilitate Aβ synthesis and buildup, and produce proinflammatory cytokines which encourage neuronal apoptosis [53, 54].

The BBB must regulate metal ion levels since they are essential for cell metabolism, transfer of signals, protein catalysis, and stability. Copper (Cu) in the body of an individual is present in either a labile form or as protein-bound, such as in ceruloplasmin and cytochrome C oxidase. Cu offers neuroprotection to neurons and glial cells through its role in maintaining neurotransmitter and neuropeptide homeostasis. An affected levels of Cu can result in excessive production of ROS and subsequent OS. This occurs through two main mechanisms: the generation of hydroxyl radicals and the reduction of glutathione (GSH), an essential antioxidant and neutralizing enzymes. Elevated concentrations of Cu can result in the suppression of Cu's catalytic activity by GSH through chelation, thus inhibiting Cu's participation in redox reactions [55].

Similarly, many biological activities that produce ROS involve iron (Fe) (Fe (II) and Fe (III)). Fe functions as a cofactor for enzymes critical to metabolic processes, particularly those related to ROS formation. Iron levels are meticulously controlled to ensure suitable intracellular concentrations [56, 57, 58].

Metal ion dysregulation has been associated with AD, where oxidative stress mediated by Aβ involves redox-active metals, especially Cu. Research suggests metals form high-affinity Aβ complexes, affecting its association and engaging in redox-cycling reactions that produce ROS, thereby triggering Aβ-induced neurotoxicity. Further study needed to comprehensively describe the underlying causes of metal-Aβ neurotoxicity; still Fe chelation therapy demonstrates potential in the management of AD [58].

Mitochondria function as a primary source of intracellular reactive substances; they are also particularly vulnerable to OS. Abnormal protein, including amyloidopathy and tauopathy, which are associated with AD can trigger apoptosis by ROS production. Research involving isolated brain tissues and mitochondria from Alzheimer's patients has revealed mitochondrial damage linked to proteinopathies encompasses interruptions in mitochondrial fusion and impaired mitophagy [59, 60]. Mitochondrial dysfunction in AD is associated with several issues, including morphological changes, a decrease in mitochondrial number, reduced ATP levels, increased ROS production, and alterations in mitochondrial cycle and synthesis [61, 62].

2.4 Ferroptosis

Fe accumulation in AD causes cellular damage, higher amyloid-beta (Aβ) aggregation and oligomerization, and promotes Tau protein hyperphosphorylation and aggregation. Fe's work in Fenton chemistry drives these consequences [57]. OS inactivates the GSH-dependent antioxidant system, causing harmful lipid-ROS to accumulate and cause ferroptosis, an iron-dependent cellular death mechanism (see Fig. 3). Ferroptosis exhibits distinct features compared to apoptosis, necrosis, and autophagy [63, 64]. Key characteristics of ferroptosis are summarized in Table 2.

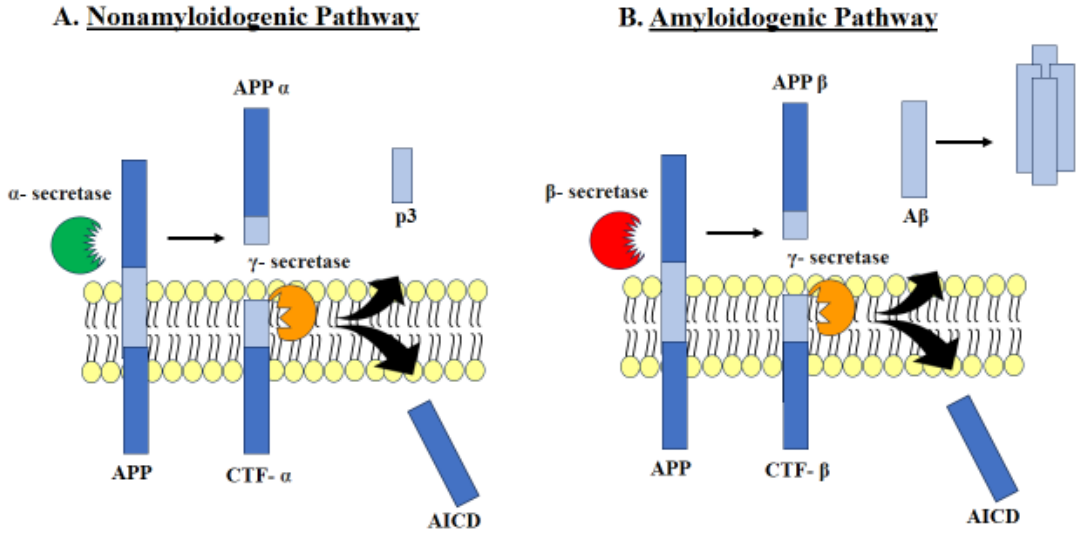

Fig. 3. Key Ferroptosis Processes: A false redox balance between iron and antioxidant systems, particularly the GSH-GPX4 pathway, damages phospholipids in the membrane and causes ferroptotic cellular death. A malfunction in GSH-biosynthesis enzyme restriction may affect the GSH-dependent GPX4 pathway. GSH

depletion inactivates GPX4, which hinders the elimination of cytotoxic lipid hydroperoxides (L-OOH), promoting free radical accumulation and hazardous lipid molecules such peroxides, causing widespread lipid peroxidation. (2) TfR1 transports Tf-bound Fe3+ to cells. Ferritin stores additional labile iron and converts Fe3+ to Fe2+ inside cells. (3) Ferritinopaghy degrades ferritin, releasing cytoplasmic iron. Free labile Fe2+ in cells increases harmful lipid ROS production largely via the Fenton reaction.

Table 1: presenting ferroptosis morphology and biochemistry:

Morphological Characteristics	Biochemical Characteristics	References
Cellular Shrinkage	**Iron Dependency**: Ferroptosis is dependent on the presence of intracellular iron.	[65]
Membrane Damage	**Lipid Peroxidation**: Accumulation of toxic lipid peroxides due to oxidative stress.	[66]
Dense Cytoplasmic Content	**Decreased Glutathione (GSH) Levels**: Reduced levels of GSH, a key antioxidant.	[67]
Loss of Cell Polarity	**Increased ROS Production**: Elevated levels of reactive oxygen species (ROS).	[68]
No Apoptotic Bodies	**Activation of Lipid Peroxidation Enzymes**: Involvement of lipoxygenases.	[69]
Mitochondrial Damage	**Inhibition of Antioxidant Enzymes**: Inactivation of GSH peroxidase and other protective enzymes.	[70]

Ferroptotic cell death is defined by three key characteristics: (i) the presence of labile redox-active iron and iron-dependent peroxidation enzymes, (ii) the role of phospholipids with polyunsaturated fatty acid tails, and (iii) the inadequate clearance of lipid-ROS [71, 72, 73].

Excessive labile Fe (II) enhances non-enzymatic lipid peroxidation through the Fenton reaction, leading to excessive ROS production and triggering ferroptosis cell death. The synthesis of the tripeptide GSH, which plays a crucial role in regulating GPX4 activity, is vital for protecting cells from ferroptosis. GSH biosynthesis is supported by the antiporter system Xc–, which exchanges glutamate and cystine and converts cystine into cysteine. GSH depletion and GPX4 inactivation result from antiporter system inhibition. In consequence of increased lipid-ROS generation, cells are more prone to ferroptosis [72, 73].

3. CONVENTIONAL DRUG THERAPIES

3.1 Approved Therapies for Alzheimer's Disease

Despite escalating AD diagnoses and socioeconomic load, there is no viable medication to reverse or stop the disease's course. Only six medications have been approved by the FDA: aducanumab, donepezil, galantamine, rivastigmine, memantine, and a combination of the two. Only aducanumab targets Aβ plaques, whereas the other five medications treat symptoms by strengthening the cholinergic system [74].

Table 2: The modes of action, molecule weights, structure-activity references, and approval dates of Alzheimer's medications:

Drug	Mechanism of Action	Molecular Weight (g/mol)	Approval Date (FDA)	Molecular Structure (References)
Aducanumab	Monoclonal antibody that targets and clears amyloid-beta (Aβ) plaques	146,000 (approximate)	June 7, 2021	[75]
Donepezil	Acetylcholinesterase inhibitor; increases acetylcholine in the brain	379.49	November 25, 1996	[76]
Galantamine	Acetylcholinesterase inhibitor and allosteric modulator of nicotinic receptors	368.44	February 28, 2001	[77]

Rivastigmine	Acetylcholinesterase and butyrylcholinesterase inhibitor	250.33	April 21, 2000	[78]
Memantine	NMDA receptor antagonist; reduces glutamatergic excitotoxicity	179.25	October 16, 2003	[79]
Memantine + Donepezil	Combined action of NMDA receptor antagonism (memantine) and cholinesterase inhibition (donepezil)	558.74 (combined)	March 2015	[80]

Aducanumab

Aducanumab, a monoclonal antibody, targets soluble β-amyloid fibrils and oligomers to eliminate Aβ plaques. At least 21 days between treatments, 10 mg/kg should be infused intravenously for an hour every four weeks [81]. In April 2021, the FDA approved aducanumab to reduce AD development by targeting senile plaques. The medication was approved after three clinical trials showed its promise.

The multicenter, PRIME trial (NCT01677572) administered 165 patients IV aducanumab (1, 3, 6, or 10 mg/kg) weekly for one year. Study demonstrated dose- and time-varying decrease in Aβ plaques and improved clinical symptoms, as measured by CDR-SB and MMSE scores at greater doses [82]. Other big phase 3, double-blind, placebo-controlled, randomized clinical trials included EMERGE (NCT02484547) and ENGAGE (NCT02477800), with 1643 and 1653 participants, respectively. The EMERGE study found that 10 mg/kg IV aducanumab monthly reduced CDR-SB scores by 22% and improved cognitive and daily function tests like MMSE, ADAS-Cog 13, and ADCS-ADL-MCI. The ENGAGE study did not confirm these findings, possibly due to variation in disease progression and the number of treatments received. Despite this, further pharmacometrics analysis linked aducanumab administration to positive responses in both studies [83].

Both phase 3 studies revealed that high-dose aducanumab (10 mg/kg) reduced amyloid deposits relative to placebo, however only the EMERGE study showed a substantial decrease in CSF tau protein content. The most prevalent adverse effect was hemosiderin accumulation, recorded in 41% of patients versus 10% in the placebo group. ARIA was usually asymptomatic and recovered [84, 85].

4. ACETYLCHOLINESTERASE INHIBITORS (ACHE)

1. Tacrine

The first FDA-approved acetylcholinesterase inhibitor (AChEI) was acridine-derived tacrine in September 1993. Acetylcholine levels rise in numerous parts of the brain as an important acetylcholinesterase inhibitor. It also inhibits pseudocholinesterase better than acetylcholinesterase. Tacrine's oral and IV administration and BBB crossing made it attractive for AD testing by Dr. Williams Summer in 1989 [86, 87]. Clinical trial outcomes were variable, casting doubt on its AD treatment efficacy. Tacrine relieved mild to moderate dementia yet did not slow neurodegeneration [88]. Tacrine was withdrawn in 2013 due to frequent side effects such loss of appetite, diarrhoea, clumsiness, and liver cytotoxicity [89].

2. Donepezil

Donepezil, a piperidine-derived cholinergic medication, inhibits acetylcholinesterase centrally and non-competitively. Besides to its primary effect, donepezil impacts AD's molecular and biological mechanisms. It suppresses glutamate-induced excitotoxicity, lowers initial inflammatory cytokines, produces a beneficial acetylcholinesterase isoform, and reduces OS [90]. Donepezil, approved in 1996 for AD, is available in oral tablet, liquid, jelly, or transdermal formulations [91]. Start with 5 mg/day and raise to 10 mg/day after 4–6 weeks. After three months on 10 mg/day, moderate to severe dementia patients can take 23 mg/day [92].

Studies have shown that donepezil at 10 mg/day improves cognitive function, daily activities, and global clinician ratings, though it does not improve behavior or quality of life [93, 94]. Higher doses (up to 23 mg/day) have not shown significant benefits over the 10 mg/day dose. Moreover, no dose of donepezil has been able to halt the progression of AD [95]. Still, the medication is usually well-tolerated with minor side effects mostly affecting the gut and nervous system [96].

3. Galantamine

The FDA approved galantamine in 2001, an selective tertiary isoquinoline alkaloid which inhibits acetylcholinesterase competitively and reversibly [97, 98]. Oral dosages of 4, 8, 12, 16, and 24 mg are given as quick-release solutions twice daily or extended-release capsules once daily. Starting at 8 mg/day, the maintenance dose can be increased to 16 mg/day after 4–8 weeks [99]. Galantamine's ability to focus on the CNS with limited peripheral activation makes it a unique AD treatment. Galantamine is coupled with ceria-containing hydroxyapatite particles, solid lipid nanoparticles, and chitosan to improve brain delivery [100, 101]. clinical trials showed that galantamine lowers agitation and abnormal movements in AD patients. In a study by Li et al. found that the medicine controls behavioral symptoms, improves daily living activities,

cognitive performance, and clinician-assessed global condition, making it a favored AD treatment [102, 103]. Galantamine is normally safe and well-tolerated, but it might produce convulsions, disorientation, muscle weakness, and moist eyes [104, 105].

4. Novel Drug Delivery Systems

Effective management of AD patients requires improving drug delivery to the brain. Recently, it gains a significant attention due to their possibility for use in treatment, diagnosis, and specified drug delivery. Typically, they ranged between 1 and 100 nm, offer unique advantages, such as increased surface area, adaptable properties, and the capacity to manage several payloads [106]. Several production methods provide exact nanoparticle structure and property control. One common method is nanoprecipitation, it includes immediately mixing a drug-containing polymer solution with a non-solvent, leading to nanoparticle precipitation [107]. This technique enhances stability and allows for controlled release, especially for hydrophobic drugs incorporated into the nanoparticle matrix. Another method is emulsion solvent evaporation, in which an organic immiscible solvent emulsifies a polymer solution, followed by solvent evaporation to form nanoparticles [108].

Electrostatic self-assembly is another approach used to create layered nanoparticles. The layer-by-layer assembly technique has the capacity to control nanoparticle release kinetics and capabilities by switching layers of different materials [109, 110].

Structural modifications to medical nanoparticles have also been examined to increase their performance. Core-shell nanoparticles, which consist of a central core and an outer shell made from different materials, improve stability, prolong circulation time, and enable controlled release of therapeutic agents [111]. Surface functionalization of nanoparticle allows selective binding to target tissues, improving transport and absorption [112].

Understanding medicinal nanoparticle composition and characteristics requires characterization. Transmission electron microscopy (TEM) reveals nanoparticle form, size, and inside structure [113]. Dynamic light scattering (DLS) measures nanoparticle range of sizes and colloidal stability in solution [114]. Nanoparticle compounding and functional groups are examined by Fourier-transform infrared spectroscopy (FTIR) [115]. X-ray diffraction (XRD) and atomic force microscopy (AFM) help study medicinal nanoparticle structure and behavior. Several clinical nanoparticles have been studied to improve BBB medication transport for neurological treatment. Table 3. These nanoparticles use unique shapes and methods to cross the BBB, enabling drug transport.

Table 3 lists nanoparticles used to breach the BBB and their principal routes of action:

Nanoparticle Type	Defining Characteristics	Main Mode of Action	References
Lipid-Based Nanoparticles	Biocompatible, non-toxic, capable of encapsulating hydrophobic drugs, with modifiable surface for targeted delivery	Cross BBB through receptor-mediated endocytosis or by enhancing permeability through lipid-soluble characteristics	[116]
Polymeric Nanoparticles	Biodegradable polymers like PLGA, customizable size, and release profile for controlled drug delivery	Cross BBB by passive diffusion or receptor-mediated endocytosis, and sustained release of drugs	[117]
Solid Lipid Nanoparticles	Solid lipid matrix at room temperature, high drug loading capacity, stable in biological fluids	Transport through BBB by passive diffusion or by adsorptive-mediated transcytosis	[118]
Dendrimers	Highly branched polymers, nanoscale size, large surface area for functionalization with targeting ligands or drugs	Cross BBB through receptor-mediated transcytosis or adsorptive-mediated transport	[119]
Gold Nanoparticles	Small size (~2-100 nm), easily functionalized with targeting molecules like peptides or antibodies	Cross BBB via endocytosis, and can be conjugated to drugs or imaging agents for targeted therapy and diagnostics	[120]
Magnetic Nanoparticles	Iron oxides, directed by magnetic fields, are ideal for imaging and administration drugs.	Cross BBB through magnetically guided transport, and often combined with targeting ligands for receptor-mediated transcytosis	[121]
Carbon	Drug distribution can be done	Cross BBB by adsorptive-mediated	[122]

Nanotubes	utilizing high-surface-area cylindrical carbon structures.	endocytosis or active transport mechanisms, potential for delivering small drugs and biomolecules	
Exosomes	Naturally occurring vesicles, biocompatible, can carry proteins, lipids, RNA, and drugs	Cross BBB via endocytosis, excellent for transporting genetic material or drugs for neurodegenerative diseases	[123]
Nanogel	Hydrogel nanoparticles with a high degree of water retention, soft and adaptable in biological systems	Cross BBB through endocytosis or adsorptive-mediated transcytosis, useful for delivering small and large molecules, including proteins and nucleic acids	[124]
Silica Nanoparticles	Highly porous, customizable surface for functionalization, good for controlled release	Cross BBB by endocytosis, useful for delivering drugs and imaging agents	[125]

5. RECENT ADVANCES AND CLINICAL TRIALS

As of January 1, 2024, there were 164 clinical trials underway for AD, including those targeting prevention, mild cognitive impairment (MCI), and AD dementia, involving 127 drugs [126, 127]. The majority of drugs are disease-modifying therapies (DMTs), with 96 DMTs making up 76% of the total drugs in clinical trials. Meanwhile, 12% (15 agents) focus on cognitive enhancement, and 13% (16 agents) address neuropsychiatric symptoms. Among the DMTs, 55% (53 agents) are small molecules, while 45% (43 agents) are biologics. Phase 3 trials consist of 66% DMTs, Phase 2 trials have 78%, and Phase 1 trials are 84% DMT-focused [127]. These pipeline agents target several key processes related to AD according to the Common Alzheimer's Disease Research Ontology (CADRO). For example, 22% target neurotransmitter receptors, 20% focus on neuroinflammation, and 18% address amyloid-beta (Aß) processes. The therapies address synaptic plasticity/neuroprotection (12%), tau-related processes (9%), metabolism and bioenergetics (6%), and other factors such as proteostasis, oxidative stress, and vascular factors [126, 127].

Among the 164 trials, 35 were newly started in 2024, comprising 9 in Phase 3, 17 in Phase 2, and 9 in Phase 1. In the past year, 37 trials concluded, 10 discontinued, 4 have been dropped, 1 was suspended, and 7 currently have an unknown status. Repurposed drugs are currently involved in 52 trials, representing 31% of existing drugs and 32% of ongoing trials. These include small molecules and biologics targeting DMT, cognitive enhancement, and therapy of neuropsychiatric symptoms. Currently, 51,398 participants are required for all trials, with 36,998 in Phase 3, 13,138 in Phase 2, and 1,262 in Phase 1. The majority (79%) of participants are involved in DMT-related trials. The U.S. is hosting 44% of the trials, while others are being conducted internationally. Likewise, four trials include cognitively healthy people at risk for AD, 42 trials target participants with mild cognitive impairment, and 49 trials involve respondents with early-stage AD. The pharmaceutical industry funds 60% of these trials [126, 127, 128, 129, 130].

table summarizing the minimal, mean, and maximal study durations for DMT biologics, DMT small molecules, based on available references:

Category	Trial Phase	Minimal Duration	Mean Duration	Maximal Duration	References
DMT Biologics	**Phase 1**	6 months	12 months	18 months	[131]
	Phase 2	12 months	24 months	36 months	[132]
	Phase 3	18 months	36 months	48 months	[132]
DMT Small Molecules	**Phase 1**	3 months	9 months	12 months	[133]
	Phase 2	9 months	18 months	24 months	[133]
	Phase 3	18 months	30 months	42 months	[134]
Cognitive Enhancing Agents	**Phase 1**	4 months	8 months	12 months	[135]
	Phase 2	6 months	16 months	24 months	[136]
	Phase 3	12 months	24 months	36 months	[136]

Neuropsychiatric Drugs	**Phase 1**	3 months	7 months	12 months	[137]
	Phase 2	6 months	12 months	18 months	[138]
	Phase 3	12 months	24 months	36 months	[138]

In 2023, the FDA approved 55 new chemical entities (NCEs) and 18 biologics across various therapeutic areas. Among these, one drug—lecanemab, an anti-amyloid monoclonal antibody (mAb)—received approval for the treatment of AD. Brexpiprazole received approval for the management of agitation related to dementia resulting from AD, although it is not a new medication, having previously been approved for other conditions [126, 127].

AD treatments have seen substantial advancements in recent years. The endorsement of aducanumab in 2021 concluded a 17-year hiatus devoid of novel AD therapies [129]. The expedited approval of lecanemab, succeeded by its complete approval in 2023, was predicated on mounting evidence indicating that the reduction of amyloid plaques, as evidenced by amyloid PET scans, correlated with a deceleration of cognitive deterioration. Donanemab is presently undergoing FDA evaluation, and the examination of its trial data may yield additional insights into the correlation between cognitive deterioration and results from amyloid and tau PET imaging [130].

In 2023, brexpiprazole, an atypical antipsychotic, became the first approved therapy for managing agitation in dementia associated with AD, representing a breakthrough for treating neuropsychiatric symptoms in AD [139]. Additionally, emerging data suggests that plasma biomarkers may soon replace amyloid PET and cerebrospinal fluid (CSF) studies for diagnosing AD, improving trial recruitment and quality by ensuring the presence of the disease in participants [140]. Transformations in the ability of biological targets, pharmacological efficacy, and biomarkers, together with changes in trial design, are anticipated to expedite the discovery of AD therapeutics. Ongoing financial support from governmental entities, advocacy organizations, philanthropic foundations, and pharmaceutical corporations is crucial to utilize this expanding knowledge and deliver novel therapies to patients.

6. CHALLENGES AND FUTURE PROSPECTS

6.1 Monoclonal antibodies as anti-AD agents

Several approaches have been offered for using mAb in immunotherapy-based anti-Aβ treatments to target and eliminate amyloid plaques associated to AD [141]. The antibody must cross the BBB and enter the brain for this approach to work [142]. It should promote macrophage/monocyte phagocytosis via Fc receptors by having a low affinity for monomers and a high affinity for accumulated amyloid [143]. Despite this, bapineuzumab along with other amyloid plaque and fibril-targeting medicines failed [144]. Cognitive function was not improved in phase 3 studies of amyloid monomer-targeting drugs such solanezumab [145]. But Table 4's anti-amyloid antibodies have shown promising Phase 2 and 3 outcomes.

ALZ-801 (tramiprosate), a selective anti-oligomer agent, signifies the next generation as it does not interact with amyloid plaques and is not linked to ARIA-E events [146]. Oral ALZ-801 is a suitable choice for at-home treatment in older people and may also be applicable for pre symptomatic persons at high risk of developing AD [147]. Aducanumab (BIIB037), a human mAbs, is undergoing assessment as a therapeutic intervention for AD. Since 2017, Biogen and Eisai Co., Ltd. have partnered for the global research and marketing of aducanumab. To evaluate its safety and effectiveness, two multicenter, double-blind, randomized, placebo-controlled, parallel-group Phase 3 studies, EMERGE and ENGAGE, were executed. Upon approval, aducanumab may become the inaugural medicine capable of potentially altering the trajectory of AD. Biogen sent in aducanumab for FDA approval in July 2020 [148, 149].

6.2 Artificial Intelligence in Alzheimer's Disease Management

AI and ML technologies in AD medical planning and simulation have improved pathophysiology and prognostic understanding of organelle interactions [150]. ML methods and ab initio simulations have improved physiological stability enabling deeper qualitative assessments and in silico simulations, enhancing neurotoxicology and neuromedicine [151]. Researchers have explored the opportunities, barriers, and prospective developments that AI and ML offer in improving AD treatment strategies and predicting toxicities, utilizing phytochemicals and innovations in plant nano-bionics [152]. NEM-based nanosensors utilized in this research are essential for monitoring plant signalling pathways and physiology, facilitating non-invasive, real-time investigations across biological and chemical components to enhance crop viability [153].

The integration of data from NEM-based tiny sensors into modern precision medicine is a novel invention that may perform the roles as agroecological strategy [154]. Growing data indicates that AD neuropathology is intricate, encompassing a range of biological processes. Consequently, treatment strategies need to be as diverse as the disease itself. Early detection, combination therapies, and lifestyle interventions are key factors in successfully addressing AD pathology [155]. Additionally, studies have demonstrated that AChE and BChE activity can be restored, antioxidant status can be improved, and elements of AD pathogenesis can be highlighted through antioxidant-enriched meals, but inadequate nutrition can

increase the chance of developing AD [156]. As previously mentioned in this review, the theory of an amyloid cascade has been the primary area of study for the last twenty years, with numerous studies mostly aiming at reducing or eliminating Aβ and senile plaques. The primary goal is to evaluate Aβ (1-42), Tau levels in the brain by the use of magnetic resonance imaging (MRI) techniques [157]. Unfortunately, amyloid-centric treatments have failed to improve patients' cognition, and Cognitive decline in AD is linked to dendritic spine abnormalities [158]. These shortcomings should be considered in future drug development, as they may represent early signs of memory circuit instability [159]. Instead of relying solely on the amyloid cascade theory, a greater focus on synaptic events is needed to understand the disease's cause. Future AD treatments will likely adopt a chemotherapy-like approach, using a method that targets many drugs and multiple targets. Still, it remains uncertain how these treatments will be tailored to specific subgroups or in what order they will be administered. Such developments could significantly shift the therapeutic landscape, including the adoption of non-amyloid approaches [159].

7. CONCLUSION

AD remains a major challenge, with no definitive cure. Recent advances in drug delivery systems, particularly those utilizing nanotechnology, have shown promise in improving the bioavailability and targeting of therapeutic agents to the brain. AI and ML innovation are making strides in understanding the disease's pathophysiology and improving diagnosis and treatment strategies. By combining innovative drug delivery methods with AI-driven diagnostics and therapeutic strategies, there is optimism that in the future, AD will be managed more effectively. The application of multi-target drug approaches, non-invasive technologies, and lifestyle modifications will likely play important role in minimizing progression of AD and improving patient outcomes. Continued research and collaboration between academic, governmental, and pharmaceutical entities are essential to capitalizing on these advancements and providing patients with better therapeutic options.

Acknowledgement

I would like to share my gratitude to all my co-authors for their contribution.

Conflict of Interest

No conflict of interest were found. All agreed to communicate the manuscript.

REFERENCES

[1] Wilson, B., & Geetha, K. M. (2020). Neurotherapeutic applications of nanomedicine for treating Alzheimer's disease. Journal of controlled release, 325, 25-37.

[2] Alzheimer's Association. (2019). 2019 Alzheimer's disease facts and figures. Alzheimer's & dementia, 15(3), 321-387.

[3] Australian Institute of Health. (2012). Dementia in Australia. AIHW.

[4] Alzheimer's Association. (2012). 2012 Alzheimer’s disease facts and figures. Alzheimer's & dementia, 8(2), 131-168.

[5] Deardorff, W. J., & Grossberg, G. T. (2016). A fixed-dose combination of memantine extended-release and donepezil in the treatment of moderate-to-severe Alzheimer’s disease. Drug design, development and therapy, 3267-3279.

[6] Shigeta, M., & Homma, A. (2001). Donepezil for Alzheimer's disease: pharmacodynamic, pharmacokinetic, and clinical profiles. CNS Drug Reviews, 7(4), 353-368.

[7] Wen, M. M., El-Salamouni, N. S., El-Refaie, W. M., Hazzah, H. A., Ali, M. M., Tosi, G., ... & Hanafy, A. S. (2017). Nanotechnology-based drug delivery systems for Alzheimer's disease management: Technical, industrial, and clinical challenges. Journal of controlled release, 245, 95-107.

[8] Vaz, M., Silva, V., Monteiro, C., & Silvestre, S. (2022). Role of aducanumab in the treatment of Alzheimer’s disease: Challenges and opportunities. Clinical interventions in aging, 797-810.

[9] Vitek, G. E., Decourt, B., & Sabbagh, M. N. (2023). Lecanemab (BAN2401): an anti–beta-amyloid monoclonal antibody for the treatment of Alzheimer disease. Expert opinion on investigational drugs, 32(2), 89-94.

[10] Singh, B., Day, C. M., Abdella, S., & Garg, S. (2024). Alzheimer's disease current therapies, novel drug delivery systems and future directions for better disease management. Journal of Controlled Release, 367, 402-424.

[11] Du, X., Wang, X., & Geng, M. (2018). Alzheimer’s disease hypothesis and related therapies. Translational neurodegeneration, 7, 1-7.

[12] Craig, L. A., Hong, N. S., & McDonald, R. J. (2011). Revisiting the cholinergic hypothesis in the

development of Alzheimer's disease. Neuroscience & Biobehavioral Reviews, 35(6), 1397-1409.

[13] Becker RE, Greig NH, Giacobini E. Why do so many drugs for Alzheimer's disease fail in development? Time for new methods and new practices? J Alzheimers Dis 2008; 15(2): 303-25

[14] Du, X., Wang, X., & Geng, M. (2018). Alzheimer's disease hypothesis and related therapies. Translational neurodegeneration, 7, 1-7.

[15] Tiwari, S., Atluri, V., Kaushik, A., Yndart, A., & Nair, M. (2019). Alzheimer's disease: pathogenesis, diagnostics, and therapeutics. International journal of nanomedicine, 5541-5554.

[16] Guo, T., Zhang, D., Zeng, Y., Huang, T. Y., Xu, H., & Zhao, Y. (2020). Molecular and cellular mechanisms underlying the pathogenesis of Alzheimer's disease. Molecular neurodegeneration, 15, 1-37.

[17] Ibrahim, M. M., & Gabr, M. T. (2019). Multitarget therapeutic strategies for Alzheimer's disease. Neural regeneration research, 14(3), 437-440.

[18] Savelieff, M. G., Nam, G., Kang, J., Lee, H. J., Lee, M., & Lim, M. H. (2018). Development of multifunctional molecules as potential therapeutic candidates for Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis in the last decade. Chemical reviews, 119(2), 1221-1322.

[19] Müller, U. C., Deller, T., & Korte, M. (2017). Not just amyloid: physiological functions of the amyloid precursor protein family. Nature Reviews Neuroscience, 18(5), 281-298.

[20] O'brien, R. J., & Wong, P. C. (2011). Amyloid precursor protein processing and Alzheimer's disease. Annual review of neuroscience, 34(1), 185-204.

[21] Thinakaran, G., & Koo, E. H. (2008). Amyloid precursor protein trafficking, processing, and function. Journal of Biological Chemistry, 283(44), 29615-29619.

[22] Carrillo-Mora, P., Luna, R., & Colín-Barenque, L. (2014). Amyloid beta: multiple mechanisms of toxicity and only some protective effects?. Oxidative medicine and cellular longevity, 2014(1), 795375.

[23] Kanaan, N. M., Himmelstein, D. S., Ward, S. M., Combs, B., & Binder, L. I. (2015). Tau protein: biology and pathobiology. In Movement Disorders (pp. 857-874). Academic Press.

[24] Iqbal, K., Alonso, A. D. C., Chen, S., Chohan, M. O., El-Akkad, E., Gong, C. X., ... & Grundke-Iqbal, I. (2005). Tau pathology in Alzheimer disease and other tauopathies. Biochimica et Biophysica Acta (BBA)-molecular basis of Disease, 1739(2-3), 198-210.

[25] Wang, J. Z., Grundke-Iqbal, I., & Iqbal, K. (2007). Kinases and phosphatases and tau sites involved in Alzheimer neurofibrillary degeneration. European Journal of Neuroscience, 25(1), 59-68.

[26] Mondragón-Rodríguez, S., Perry, G., Luna-Muñoz, J., Acevedo-Aquino, M. C., & Williams, S. (2014). Phosphorylation of tau protein at sites Ser 396–404 is one of the earliest events in A lzheimer's disease and D own syndrome. Neuropathology and applied neurobiology, 40(2), 121-135.

[27] Yang, K., Chen, Z., Gao, J., Shi, W., Li, L., Jiang, S., ... & Wu, L. (2017). The key roles of GSK-3β in regulating mitochondrial activity. Cellular Physiology and Biochemistry, 44(4), 1445-1459.

[28] Souder, D. C., & Anderson, R. M. (2019). An expanding GSK3 network: implications for aging research. Geroscience, 41(4), 369-382.

[29] Ito, F., Sono, Y., & Ito, T. (2019). Measurement and clinical significance of lipid peroxidation as a biomarker of oxidative stress: oxidative stress in diabetes, atherosclerosis, and chronic inflammation. Antioxidants, 8(3), 72.

[30] Forman, H. J., & Zhang, H. (2021). Targeting oxidative stress in disease: promise and limitations of antioxidant therapy. Nature Reviews Drug Discovery, 20(9), 689-709.

[31] Circu, M. L., & Aw, T. Y. (2010). Reactive oxygen species, cellular redox systems, and apoptosis. Free radical biology and medicine, 48(6), 749-762.

[32] Zhao, Y., & Zhao, B. (2013). Oxidative stress and the pathogenesis of Alzheimer′ s disease. Oxidative medicine and cellular longevity, 2013(1), 316523.

[33] Ganguly, G., Chakrabarti, S., Chatterjee, U., & Saso, L. (2017). Proteinopathy, oxidative stress and mitochondrial dysfunction: cross talk in Alzheimer's disease and Parkinson's disease. Drug design, development and therapy, 797-810.

[34] Butterfield, D. A., & Boyd-Kimball, D. (2004). Amyloid β-Peptide (1-42) Contributes to the oxidative stress and neurodegeneration found in Alzheimer disease brain. Brain Pathology, 14(4), 426-432.

[35] Boyd-Kimball, D., Sultana, R., Poon, H. F., Lynn, B. C., Casamenti, F., Pepeu, G., ... & Butterfield, D. A. (2005). Proteomic identification of proteins specifically oxidized by intracerebral injection of amyloid β-peptide (1–42) into rat brain: implications for Alzheimer's disease. Neuroscience, 132(2), 313-324.

[36] Cai, Z., Zhao, B., & Ratka, A. (2011). Oxidative stress and β-amyloid protein in Alzheimer's disease. Neuromolecular medicine, 13, 223-250.

[37] Shelat, P. B., Chalimoniuk, M., Wang, J. H., Strosznajder, J. B., Lee, J. C., Sun, A. Y., ... & Sun, G. Y. (2008). Amyloid beta peptide and NMDA induce ROS from NADPH oxidase and AA release from cytosolic phospholipase A2 in cortical neurons. Journal of neurochemistry, 106(1), 45-55.

[38] Huang, X., Moir, R. D., Tanzi, R. E., Bush, A. I., & Rogers, J. T. (2004). Redox-active metals, oxidative stress, and Alzheimer's disease pathology. Annals of the New York Academy of Sciences, 1012(1), 153-163.

[39] Butterfield, D. A., Di Domenico, F., Swomley, A. M., Head, E., & Perluigi, M. (2014). Redox proteomics analysis to decipher the neurobiology of Alzheimer-like neurodegeneration: overlaps in Down's syndrome and Alzheimer's disease brain. Biochemical Journal, 463(2), 177-189.

[40] Butterfield, D. A., Swomley, A. M., & Sultana, R. (2013). Amyloid β-peptide (1–42)-induced oxidative stress in Alzheimer disease: importance in disease pathogenesis and progression. Antioxidants & redox signaling, 19(8), 823-835.

[41] Rinaldi, C., Donato, L., Alibrandi, S., Scimone, C., D'Angelo, R., & Sidoti, A. (2021). Oxidative stress and the neurovascular unit. Life, 11(8), 767.

[42] Colonna, M., & Butovsky, O. (2017). Microglia function in the central nervous system during health and neurodegeneration. Annual review of immunology, 35(1), 441-468.

[43] Hansen, D. V., Hanson, J. E., & Sheng, M. (2018). Microglia in Alzheimer's disease. Journal of Cell Biology, 217(2), 459-472.

[44] Kwon, H. S., & Koh, S. H. (2020). Neuroinflammation in neurodegenerative disorders: the roles of microglia and astrocytes. Translational neurodegeneration, 9(1), 42.

[45] Juźwik, C. A., Drake, S. S., Zhang, Y., Paradis-Isler, N., Sylvester, A., Amar-Zifkin, A., ... & Fournier, A. E. (2019). microRNA dysregulation in neurodegenerative diseases: A systematic review. Progress in neurobiology, 182, 101664.

[46] Acioglu, C., Li, L., & Elkabes, S. (2021). Contribution of astrocytes to neuropathology of neurodegenerative diseases. Brain research, 1758, 147291.

[47] Escartin, C., Galea, E., Lakatos, A., O'Callaghan, J. P., Petzold, G. C., Serrano-Pozo, A., ... & Verkhratsky, A. (2021). Reactive astrocyte nomenclature, definitions, and future directions. Nature neuroscience, 24(3), 312-325.

[48] Sarkar, S., & Biswas, S. C. (2021). Astrocyte subtype-specific approach to Alzheimer's disease treatment. Neurochemistry International, 145, 104956.

[49] Arranz, A. M., & De Strooper, B. (2019). The role of astroglia in Alzheimer's disease: pathophysiology and clinical implications. The Lancet Neurology, 18(4), 406-414.

[50] Hong, P., Zhang, X., Gao, S., & Wang, P. (2020). Role of monocarboxylate transporter 4 in Alzheimer disease. Neurotoxicology, 76, 191-199.

[51] Liu, B., Teschemacher, A. G., & Kasparov, S. (2017). Neuroprotective potential of astroglia. Journal of Neuroscience Research, 95(11), 2126-2139.

[52] Veyrat-Durebex, C., Corcia, P., Piver, E., Devos, D., Dangoumau, A., Gouel, F., ... & Blasco, H. (2016). Disruption of TCA cycle and glutamate metabolism identified by metabolomics in an in vitro model of amyotrophic lateral sclerosis. Molecular neurobiology, 53, 6910-6924.

[53] Perez-Nievas, B. G., & Serrano-Pozo, A. (2018). Deciphering the astrocyte reaction in Alzheimer's disease. Frontiers in Aging Neuroscience, 10, 114.

[54] Walker, K. A., Ficek, B. N., & Westbrook, R. (2019). Understanding the role of systemic inflammation in Alzheimer's disease. ACS chemical neuroscience, 10(8), 3340-3342.

[55] Jomova, K., Baros, S., & Valko, M. (2012). Redox active metal-induced oxidative stress in biological systems. Transition Metal Chemistry, 37, 127-134.

[56] Gammella, E., Buratti, P., Cairo, G., & Recalcati, S. (2017). The transferrin receptor: the cellular iron gate. Metallomics, 9(10), 1367-1375.

[57] Nakamura, T., Naguro, I., & Ichijo, H. (2019). Iron homeostasis and iron-regulated ROS in cell death, senescence and human diseases. Biochimica et Biophysica Acta (BBA)-General Subjects, 1863(9), 1398-1409.

[58] Wessling-Resnick, M. (2018). Crossing the iron gate: why and how transferrin receptors mediate viral entry. Annual review of nutrition, 38(1), 431-458.

[59] Wang, X., Su, B. O., Lee, H. G., Li, X., Perry, G., Smith, M. A., & Zhu, X. (2009). Impaired balance of mitochondrial fission and fusion in Alzheimer's disease. Journal of neuroscience, 29(28), 9090-9103.

[60] Devi, L., Prabhu, B. M., Galati, D. F., Avadhani, N. G., & Anandatheerthavarada, H. K. (2006). Accumulation of amyloid precursor protein in the mitochondrial import channels of human Alzheimer's disease brain is associated with mitochondrial dysfunction. Journal of Neuroscience, 26(35), 9057-9068.

[61] Cenini, G., & Voos, W. (2019). Mitochondria as potential targets in Alzheimer disease therapy: an update. Frontiers in pharmacology, 10, 902.

[62] Sharma, C., & Kim, S. R. (2021). Linking oxidative stress and proteinopathy in Alzheimer's disease. Antioxidants, 10(8), 1231.

[63] Cao, J. Y., & Dixon, S. J. (2016). Mechanisms of ferroptosis. Cellular and Molecular Life Sciences, 73, 2195-2209.

[64] Han, C., Liu, Y., Dai, R., Ismail, N., Su, W., & Li, B. (2020). Ferroptosis and its potential role in human diseases. Frontiers in pharmacology, 11, 239.

[65] Yu, H., Guo, P., Xie, X., Wang, Y., & Chen, G. (2017). Ferroptosis, a new form of cell death, and its relationships with tumourous diseases. Journal of cellular and molecular medicine, 21(4), 648-657.

[66] Feng, H., & Stockwell, B. R. (2018). Unsolved mysteries: How does lipid peroxidation cause ferroptosis?. PLoS biology, 16(5), e2006203.

[67] Kuang, F., Liu, J., Tang, D., & Kang, R. (2020). Oxidative damage and antioxidant defense in ferroptosis. Frontiers in cell and developmental biology, 8, 586578.

[68] Kuang, F., Liu, J., Tang, D., & Kang, R. (2020). Oxidative damage and antioxidant defense in ferroptosis. Frontiers in cell and developmental biology, 8, 586578.

[69] Su, L. J., Zhang, J. H., Gomez, H., Murugan, R., Hong, X., Xu, D., ... & Peng, Z. Y. (2019). Reactive oxygen species-induced lipid peroxidation in apoptosis, autophagy, and ferroptosis. Oxidative medicine and cellular longevity, 2019(1), 5080843.

[70] Kajarabille, N., & Latunde-Dada, G. O. (2019). Programmed cell-death by ferroptosis: antioxidants as mitigators. International journal of molecular sciences, 20(19), 4968.

[71] Stockwell, B. R., & Jiang, X. (2020). The chemistry and biology of ferroptosis. Cell chemical biology, 27(4), 365-375.

[72] Yu, Y., Yan, Y., Niu, F., Wang, Y., Chen, X., Su, G., ... & Xiong, Y. (2021). Ferroptosis: a cell death connecting oxidative stress, inflammation and cardiovascular diseases. Cell death discovery, 7(1), 193.

[73] Li, J., Cao, F., Yin, H. L., Huang, Z. J., Lin, Z. T., Mao, N., ... & Wang, G. (2020). Ferroptosis: past, present and future. Cell death & disease, 11(2), 88.

[74] Singh, B., Day, C. M., Abdella, S., & Garg, S. (2024). Alzheimer's disease current therapies, novel drug delivery systems and future directions for better disease management. Journal of Controlled Release, 367, 402-424.

[75] Heidebrink, J. L., & Paulson, H. L. (2024). Lessons Learned from Approval of Aducanumab for Alzheimer's Disease. Annual Review of Medicine, 75(1), 99-111.

[76] Nham, T., Garcia, M. C., Tsang, K. L. J., Silva, J. M., Schneider, T., Deng, J., ... & Holbrook, A. (2024). Proarrhythmic major adverse cardiac events with donepezil: A systematic review with meta-analysis. Journal of the American Geriatrics Society.

[77] D'Arrigo, T. (2024). MedCheck: Zunveyl for Alzheimer's, Erzofri for Schizophrenia, Gene Therapy and Parkinson's, and more.

[78] Chiew, A. L., Holford, A. G., Chan, B. S., & Isoardi, K. Z. (2024). Rivastigmine for the management of anticholinergic delirium. Clinical Toxicology, 62(2), 82-87.

[79] Tari, P. K., Parsons, C. G., Collingridge, G. L., & Rammes, G. (2024). Memantine: updating a rare success story in pro-cognitive therapeutics. Neuropharmacology, 244, 109737.

[80] Yaghmaei, E., Lu, H., Ehwerhemuepha, L., Zheng, J., Danioko, S., Rezaie, A., ... & Rakovski, C. (2024). Combined use of Donepezil and Memantine increases the probability of five-year survival of Alzheimer's disease patients. Communications Medicine, 4(1), 99.

[81] Martins, A. C., Oshiro, M. Y., Albericio, F., & de la Torre, B. G. (2024). Food and Drug Administration (FDA) Approvals of Biological Drugs in 2023. Biomedicines, 12(9), 1992.

[82] Pizzo, M. E., Plowey, E. D., Khoury, N., Kwan, W., Abettan, J., DeVos, S. L., ... & Zuchero, Y. J. Y. (2024). Engineering anti-amyloid antibodies with transferrin receptor targeting improves brain biodistribution and

mitigates ARIA. bioRxiv, 2024-07.

[83] Biogen A Phase 3 Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Aducanumab (BIIB037) in Subjects With Early Alzheimer's Disease. 2021. Available online: clinicaltrials.gov.

[84] Biogen. 221AD302 Phase 3 Study of Aducanumab (BIIB037) in Early Alzheimer's Disease—Tabular View—ClinicalTrials.Gov. 2021. Available online: https://clinicaltrials.gov/ct2/show/NCT02484547.

[85] Wilhelmsen, K. C., D'Haese, P. F., Haut, M. W., Marano, G. D., Mehta, R. I., Wang, X., ... & Rezai, A. (2024). Metabolism as a biomarker for treatment success in anti-amyloid therapy: A case report. Neuroimage: Reports, 4(2), 100203.

[86] Romero-Ramírez, L., & Mey, J. (2024). Emerging Roles of Bile Acids and TGR5 in the Central Nervous System: Molecular Functions and Therapeutic Implications. International Journal of Molecular Sciences, 25(17), 9279.

[87] Arjmandi-Rad, S., Vestergaard Nieland, J. D., Goozee, K. G., & Vaseghi, S. (2024). The effects of different acetylcholinesterase inhibitors on EEG patterns in patients with Alzheimer's disease: A systematic review. Neurological Sciences, 45(2), 417-430.

[88] Giri, M., Kendre, P. N., Bhalke, R., Pande, V., Autade, K., & Sumbe, R. (2024). Combinatorial therapy in Alzheimer's disease. In Alzheimer's Disease and Advanced Drug Delivery Strategies (pp. 439-461). Academic Press.

[89] Huang, S. T., Luo, J. C., Zhong, G. H., Teng, L. P., Yang, C. Y., Tang, C. L., ... & Jiang, N. (2024). In vitro and in vivo Biological Evaluation of Newly Tacrine-Selegiline Hybrids as Multi-Target Inhibitors of Cholinesterases and Monoamine Oxidases for Alzheimer's Disease. Drug Design, Development and Therapy, 133-159.

[90] Fan, G., Pan, T., Ji, X., Jiang, C., Wang, F., Liu, X., ... & Le, Q. (2024). Paternal Preconception Donepezil Exposure Enhances Learning in Offspring.

[91] Drapaca, C. S. (2024). Mathematical Modeling of Alzheimer's Drug Donepezil Hydrochloride Transport to the Brain after Oral Administration. Fractal and Fractional, 8(9), 496.

[92] Meziou, L., & Haubrick, K. (2024). A Systematic Review of the Effectiveness of Acetylcholinesterase Inhibitors on Cognition for Patients with Alzheimer's Disease. Research Review, 5(6).

[93] Jeon, J. H., Jeon, S. Y., Baek, Y. J., Park, C. E., Choi, M. K., Han, Y. T., & Song, I. S. (2024). Pharmacokinetics and Enterohepatic Circulation of 2-(Quinoline-8-carboxamido) benzoic Acid (2-QBA) in Mice. Pharmaceutics, 16(7).

[94] Kumar, S., Singh, S., Rajput, D., Sharma, B., Chaturvedi, K., Singh, N., ... & Mukherjee, S. (2024). Pharmacological Approaches and Herbal Interventions for Alzheimer's Disease. The Natural Products Journal, 14(8), 39-54.

[95] Sheikh, M., & Ammar, M. (2024). Efficacy of 5 and 10 mg donepezil in improving cognitive function in patients with dementia: a systematic review and meta-analysis. Frontiers in Neuroscience, 18, 1398952.

[96] Shukla, D., Suryavanshi, A., Bharti, S. K., Asati, V., & Kar Mahapatra, D. (2024). Recent Advances in the Treatment and Management of Alzheimer's Disease: A Precision Medicine Perspective. Current Topics in Medicinal Chemistry.

[97] Atanasova, M., Stavrakov, G., Philipova, I., Georgiev, B., Bastida, J., Doytchinova, I., & Berkov, S. (2024). AChE inhibitory activity of N-substituted natural galanthamine derivatives. Bioorganic & Medicinal Chemistry Letters, 129937.

[98] Abukuri, D. N. (2024). Evidenced-based biological prevention and intervention strategies of dementia: a narrative review. Current Psychology, 43(10), 8799-8811.

[99] Shadab, S., Rao, G. S. N., Paliwal, D., Yadav, D., Alam, A., Singh, A., & Sultana, M. J. (2024). A Comprehensive Review of Herbal Medicines for the Treatment of Alzheimer's Disease. Current Traditional Medicine, 10(5), 98-116.

[100] Elmahboub, Y. S., & Elkordy, A. A. (2024). Polymeric nanoparticles: A promising strategy for treatment of Alzheimer's disease. Journal of Taibah University Medical Sciences, 19(3), 549-565.

[101] Gawade, A., Polshettiwar, S., Hingalajia, H., Prajapati, B. G., & Singh, A. (2024). Pharmacokinetics and pharmacodynamics of various novel formulations targeting Alzheimer's disease. In Alzheimer's Disease and Advanced Drug Delivery Strategies (pp. 391-402). Academic Press.

[102] Wahba, S.M.; Darwish, A.S.; Kamal, S.M. Ceria-containing uncoated and coated hydroxyapatite-based

galantamine nanocomposites for formidable treatment of Alzheimer's disease in ovariectomized albino-rat model. Mater. Sci. Eng. C Mater. Biol. Appl. 2016, 65, 151–163

[103] Hornung, K. A. (2024). The influence of neprilysin on the pathogenesis of sporadic Alzheimer's disease.

[104] Syeed, R., Mujib, A., Bansal, Y., Mohsin, M., Nafees, A., Malik, M. Q., ... & Magyar-Tábori, K. (2024). Tissue-Specific Natural Synthesis of Galanthaminein Zephyranthes Species and Its Accumulation in Different In Vitro-Grown Organs Following Methyl Jasmonate Treatment. Plants, 13(14).

[105] Yaghmaei, E., Lu, H., Ehwerhemuepha, L., Zheng, J., Danioko, S., Rezaie, A., ... & Rakovski, C. (2024). Combined use of Donepezil and Memantine increases the probability of five-year survival of Alzheimer's disease patients. Communications Medicine, 4(1), 99.

[106] Farokhzad, O. C., & Langer, R. (2009). Impact of nanotechnology on drug delivery. ACS nano, 3(1), 16-20.

[107] Gaucher, G., Dufresne, M. H., Sant, V. P., Kang, N., Maysinger, D., & Leroux, J. C. (2005). Block copolymer micelles: preparation, characterization and application in drug delivery. Journal of controlled release, 109(1-3), 169-188.

[108] Govender, T., Stolnik, S., Garnett, M. C., Illum, L., & Davis, S. S. (1999). PLGA nanoparticles prepared by nanoprecipitation: drug loading and release studies of a water soluble drug. Journal of controlled release, 57(2), 171-185.

[109] Lvov, Y., Haas, H., Decher, G., Moehwald, H., & Kalachev, A. (1993). Assembly of polyelectrolyte molecular films onto plasma-treated glass. The Journal of Physical Chemistry, 97(49), 12835-12841.

[110] Caruso, F., Caruso, R. A., & Mohwald, H. (1998). Nanoengineering of inorganic and hybrid hollow spheres by colloidal templating. Science, 282(5391), 1111-1114.

[111] Torchilin, V. P. (2006). Nanoparticulates as drug carriers. Imperial college press.

[112] Mensah, M. B., Awudza, J. A., & O'Brien, P. (2018). Castor oil: A suitable green source of capping agent for nanoparticle syntheses and facile surface functionalization. Royal Society Open Science, 5(8), 180824.

[113] Malatesta, M. (2021). Transmission electron microscopy as a powerful tool to investigate the interaction of nanoparticles with subcellular structures. International Journal of Molecular Sciences, 22(23), 12789.

[114] Berne, B. J., & Pecora, R. (2000). Dynamic light scattering: with applications to chemistry, biology, and physics. Courier Corporation.

[115] Mourdikoudis, S., Pallares, R. M., & Thanh, N. T. (2018). Characterization techniques for nanoparticles: comparison and complementarity upon studying nanoparticle properties. Nanoscale, 10(27), 12871-12934.

[116] Zhao, Y., Gan, L., Ren, L., Lin, Y., Ma, C., & Lin, X. (2022). Factors influencing the blood-brain barrier permeability. Brain research, 1788, 147937.

[117] Govender, T., Stolnik, S., Garnett, M. C., Illum, L., & Davis, S. S. (1999). PLGA nanoparticles prepared by nanoprecipitation: drug loading and release studies of a water soluble drug. Journal of controlled release, 57(2), 171-185.

[118] Müller, M. B., Keck, M. E., Binder, E. B., Kresse, A. E., Hagemeyer, T. P., Landgraf, R., ... & Uhr, M. (2003). ABCB1 (MDR1)-type P-glycoproteins at the blood–brain barrier modulate the activity of the hypothalamic–pituitary–adrenocortical system: implications for affective disorder. Neuropsychopharmacology, 28(11), 1991-1999.

[119] van den Broek, S. L., Shalgunov, V., & Herth, M. M. (2022). Transport of nanomedicines across the blood-brain barrier: Challenges and opportunities for imaging and therapy. Biomaterials advances, 141, 213125.

[120] Hainfeld, J. F., Slatkin, D. N., & Smilowitz, H. M. (2004). The use of gold nanoparticles to enhance radiotherapy in mice. Physics in Medicine & Biology, 49(18), N309.

[121] Pankhurst, Q. A., Connolly, J., Jones, S. K., & Dobson, J. (2003). Applications of magnetic nanoparticles in biomedicine. Journal of physics D: Applied physics, 36(13), R167.

[122] Liu, C., & Cheng, H. M. (2013). Carbon nanotubes: Controlled growth and application. Materials Today, 16(1-2), 19-28.

[123] Lakhal, S., & Wood, M. J. (2011). Exosome nanotechnology: an emerging paradigm shift in drug delivery: exploitation of exosome nanovesicles for systemic in vivo delivery of RNAi heralds new horizons for drug delivery across biological barriers. Bioessays, 33(10), 737-741.

[124] Oh, J. K., Lee, D. I., & Park, J. M. (2009). Biopolymer-based microgels/nanogels for drug delivery applications. Progress in polymer science, 34(12), 1261-1282.

[125] Kim, T. W., Chung, P. W., Slowing, I. I., Tsunoda, M., Yeung, E. S., & Lin, V. S. Y. (2008). Structurally

ordered mesoporous carbon nanoparticles as transmembrane delivery vehicle in human cancer cells. Nano letters, 8(11), 3724-3727.

[126] 2023 Alzheimer's disease facts and figures. Alzheimers Dement. 2023;19:1598-1695

[127] Cummings, J., Zhou, Y., Lee, G., Zhong, K., Fonseca, J., & Cheng, F. (2024). Alzheimer's disease drug development pipeline: 2024. Alzheimer's & Dementia: Translational Research & Clinical Interventions, 10(2), e12465.

[128] Jansen, W. J., Ossenkoppele, R., Knol, D. L., Tijms, B. M., Scheltens, P., Verhey, F. R., ... & Amyloid Biomarker Study Group. (2015). Prevalence of cerebral amyloid pathology in persons without dementia: a meta-analysis. Jama, 313(19), 1924-1938.

[129] Budd Haeberlein, S., Aisen, P. S., Barkhof, F., Chalkias, S., Chen, T., Cohen, S., ... & Sandrock, A. (2022). Two randomized phase 3 studies of aducanumab in early Alzheimer's disease. The journal of prevention of Alzheimer's disease, 9(2), 197-210.

[130] Sims, J. R., Zimmer, J. A., Evans, C. D., Lu, M., Ardayfio, P., Sparks, J., ... & Kaul, S. (2023). Donanemab in early symptomatic Alzheimer disease: the TRAILBLAZER-ALZ 2 randomized clinical trial. Jama, 330(6), 512-527.

[131] Jain, S., Singh, R., Paliwal, S., & Sharma, S. (2023). Targeting Neuroinflammation as Disease Modifying Approach to Alzheimer's Disease: Potential and Challenges. Mini Reviews in Medicinal Chemistry, 23(22), 2097-2116.

[132] Buccellato, F. R., D'Anca, M., Tartaglia, G. M., Del Fabbro, M., Scarpini, E., & Galimberti, D. (2023). Treatment of Alzheimer's disease: beyond symptomatic therapies. International Journal of Molecular Sciences, 24(18), 13900.

[133] Cao, Y., Yu, F., Lyu, Y., & Lu, X. (2022). Promising candidates from drug clinical trials: Implications for clinical treatment of Alzheimer's disease in China. Frontiers in Neurology, 13, 1034243.

[134] Perneczky, R., Jessen, F., Grimmer, T., Levin, J., Flöel, A., Peters, O., & Froelich, L. (2023). Anti-amyloid antibody therapies in Alzheimer's disease. Brain, 146(3), 842-849.

[135] Xiao, S., Chan, P., Wang, T., Hong, Z., Wang, S., Kuang, W., ... & Zhang, Z. (2021). A 36-week multicenter, randomized, double-blind, placebo-controlled, parallel-group, phase 3 clinical trial of sodium oligomannate for mild-to-moderate Alzheimer's dementia. Alzheimer's Research & Therapy, 13, 1-11.

[136] Huang, L. K., Kuan, Y. C., Lin, H. W., & Hu, C. J. (2023). Clinical trials of new drugs for Alzheimer disease: a 2020–2023 update. Journal of Biomedical Science, 30(1), 83.

[137] Pleen, J., & Townley, R. (2022). Alzheimer's disease clinical trial update 2019–2021. Journal of Neurology, 269(2), 1038-1051.

[138] Gonzales, M. M., Garbarino, V. R., Kautz, T. F., Palavicini, J. P., Lopez-Cruzan, M., Dehkordi, S. K., ... & Orr, M. E. (2023). Senolytic therapy in mild Alzheimer's disease: a phase 1 feasibility trial. Nature medicine, 29(10), 2481-2488.

[139] Lee D, Slomkowski M, Hefting N, et al. Brexpiprazole for the treatment of agitation in Alzheimer dementia: A randomized clinical trial. JAMA Neurol. 2023;80(12):1307-1316

[140] Mila-Aloma M, Ashton NJ, Shekari M, et al. Plasma p-tau231 and p-tau217 as state markers of amyloid-beta pathology in preclinical Alzheimer's disease. Nat Med. 2022;28:1797-1801.

[141] Sevigny J, Chiao P, Bussière T, Weinreb PH, Williams L, Maier M, et al. The antibody aducanumab reduces Aβ plaques in Alzheimer's disease. Nature. 2016;537(7618):50-6. doi: 10.1038/nature19323, PMID 27582220.

[142] Bohrmann B, Baumann K, Benz J, Gerber F, Huber W, Knoflach F, et al. Gantenerumab: a novel human anti-Aβ antibody demonstrates sustained cerebral amyloid-β binding and elicits cell-mediated removal of human amyloid-β. J Alzheimers Dis. 2012;28(1):49-69. doi: 10.3233/JAD-2011-110977, PMID 21955818.

[143] Logovinsky V, Satlin A, Lai R, Swanson C, Kaplow J, Osswald G, et al. Safety and tolerability of BAN2401-a clinical study in Alzheimer's disease with a protofibril selective Aβ antibody. Alzheimers Res Ther. 2016;8(1):14. doi: 10.1186/s13195-016- 0181-2, PMID 27048170.

[144] Salloway S, Sperling R, Fox NC, Blennow K, Klunk W, Raskind M, et al. Two phase 3 trials of Bapineuzumab in mild-to-moderate Alzheimer's disease. N Engl J Med. 2014;370(4):322-33. doi: 10.1056/NEJMoa1304839, PMID 24450891.

[145] Honig LS, Vellas B, Woodward M, Boada M, Bullock R, Borrie M, et al. Trial of solanezumab for mild dementia due to Alzheimer's disease. N Engl J Med. 2018;378(4):321-30. doi: 10.1056/NEJMoa1705971,

PMID 29365294.

[146] Schneider L. A resurrection of aducanumab for Alzheimer's disease. Lancet Neurol. 2020;19(2):111-2. doi: 10.1016/S1474-4422(19)30480-6, PMID 31978357. 90.

[147] Kocis P, Tolar M, Yu J, Sinko W, Ray S, Blennow K, et al. Elucidating the Aβ42 anti-aggregation mechanism of action of tramiprosate in Alzheimer's disease: integrating molecular analytical methods, pharmacokinetic and clinical data. CNS Drugs. 2017;31(6):495-509. doi: 10.1007/s40263-017-0434-z, PMID 28435985. 91.

[148] Tolar M, Abushakra S, Hey JA, Porsteinsson A, Sabbagh M. Aducanumab, gantenerumab, BAN2401, and ALZ-801—the first wave of amyloid-targeting drugs for Alzheimer's disease with potential for near term approval. Alzheimers Res Ther. 2020;12(1):95. doi: 10.1186/s13195-020-00663-w, PMID 32787971. 92.

[149] Mukhopadhyay S, Banerjee D. A primer on the evolution of aducanumab: the first antibody approved for treatment of Alzheimer's disease. J Alzheimers Dis. 2021;83(4):1537-52. doi: 10.3233/JAD-215065, PMID 34366359. 93.

[150] Singh AV, Ansari MHD, Rosenkranz D, Maharjan RS, Kriegel FL, Gandhi K, et al. Artificial intelligence and machine learning in computational nanotoxicology: unlocking and empowering nanomedicine. Adv Healthc Mater. 2020;9(17):e1901862. doi: 10.1002/ adhm.201901862, PMID 32627972. 94.

[151] Singh AV, Maharjan RS, Kanase A, Siewert K, Rosenkranz D, Singh R, et al. Machine-learning-based approach to decode the influence of nanomaterial properties on their interaction with cells. ACS Appl Mater Interfaces. 2021;13(1):1943-55. doi: 10.1021/acsami.0c18470, PMID 33373205

[152] Borderud SP, Li Y, Burkhalter JE, Sheffer CE, Ostroff JS. Electronic cigarette uses among patients with cancer: characteristics of electronic cigarette users and their smoking cessation outcomes. Cancer. 2014;120(22):3527-35. doi: 10.1002/cncr.288 11, PMID 25252116. 96.

[153] Ansari MHD, Lavhale S, Kalunke RM, Srivastava PL, Pandit V, Gade S, et al. Recent advances in plant nanobionics and nanobiosensors for toxicology applications. Curr Nanosci. 2020;16(1):27-41. doi: 10.2174/1573413715666190409101305. 97.

[154] Tiwari Pandey A, Pandey I, Zamboni P, Gemmati D, Kanase A, Singh AV, et al. Traditional herbal remedies with a multifunctional therapeutic approach as an implication in COVID-19 associated co-infections. Coatings. 2020;10(8):761. doi: 10 .3390/coatings10080761. 98.

[155] Vikram Singh A, Sigloch H, Laux P, Luch A, Wagener S, Tentschert J. Micro/nanoplastics: an emerging environmental concern for the future decade. Front Nanosci Nanotech. 2021;7(1):1-2. doi: 10.15761/FNN.1000191. 99.

[156] Kamphuis PJGH, Scheltens P. Can nutrients prevent or delay onset of Alzheimer's disease? J Alzheimers Dis. 2010;20(3):765-75. doi: 10.3233/JAD-2010-091558, PMID 20182021. 100.

[157] Agunloye OM, Oboh G, Falade AO. Pleurotus ostreatus and Lentinus subnudus supplemented diets restore altered acetylcholinesterase and butyrylcholinesterase activities and improve antioxidant status in transgenic Drosophila melanogaster model. J Diet Suppl. 2021;18(4):372-86. doi: 10.1080/19390211.2020.1772441, PMID 32496927. 101.

[158] Falcon C, Tucholka A, Monté-Rubio GC, Cacciaglia R, Operto G, Rami L, et al. Longitudinal structural cerebral changes related to core CSF biomarkers in preclinical Alzheimer's disease: A study of two independent datasets. NeuroImage Clin. 2018;19:190-201. doi: 10.1016/j.nicl.2018.04.016, PMID 30023169. 102.

[159] Counts SE, Ikonomovic MD, Mercado N, Vega IE, Mufson EJ. Biomarkers for the early detection and progression of Alzheimer's disease. Neurotherapeutics. 2017;14(1):35-53. doi: 10.1007/s13311-016-0481-z, PMID 27738903