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REVIEW ARTICLE

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Antineoplastics for treating Alzheimer's disease and dementia: Evidence from preclinical and observational studies

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Abstract

As the world population ages, there will be an increasing need for effective therapies for aging-associated neurodegenerative disorders, which remain untreatable. Dementia due to Alzheimer's disease (AD) is one of the leading neurological diseases in the aging population. Current therapeutic approaches to treat this disorder are solely symptomatic, making the need for new molecular entities acting on the causes of the disease extremely urgent. One of the potential solutions is to use compounds that are already in the market. The structures have known pharmacokinetics, pharmacodynamics, toxicity profiles, and patient data available in several countries. Several drugs have been used successfully to treat diseases different from their original purposes, such as autoimmunity and peripheral inflammation. Herein, we divulge the repurposing of drugs in the area of neurodegenerative diseases, focusing on the therapeutic potential of antineoplastics to treat dementia due to AD and dementia. We briefly touch upon the shared pathological mechanism between AD and cancer and drug repurposing strategies, with a focus on artificial intelligence. Next, we bring out the

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current status of research on the development of drugs, provide supporting evidence from retrospective, clinical, and preclinical studies on antineoplastic use, and bring in new areas, such as repurposing drugs for the prion-like spreading of pathologies in treating AD.

KEYWORDS

aging, Alzheimer's disease, antineoplastic, dementia, drug repurposing, neurodegenerative diseases

1 | INTRODUCTION–DEMENTIA AND ALZHEIMER'S DISEASE

Dementia is one of the leading causes of aging-associated impairment in cognitive functions of individuals, leading in most cases to complete dependence on caregivers. Currently, over 55 million people worldwide live with dementia, which is expected to double by 2050.[1] The percentage change in the total number of dementia cases between 2019 and 2050 is expected to be the highest among countries with a low socio-demographic index (SDI), and the increase in dementia cases in most countries, irrespective of SDI, is associated with population growth and aging.[1] Among neurodegenerative disorders (NDDs) that present with dementia, Alzheimer's disease (AD) accounts for 60-80% of cases worldwide.[2]

Complex brain changes occur over decades in the sporadic or late-onset form of AD patients over 60. However, early symptoms are typically associated with impaired cognition, followed by other signs that develop based on the disease stage.[3] Women are more susceptible to AD than men, and this sex-specific difference in the prevalence could be linked to the mechanisms of neuroinflammation that differ between genders.[4,5] The Lancet Commission has identified several modifiable risk factors for dementia, such as *poor levels of education*, *high blood pressure*, *hearing loss*, *smoking*, *obesity*, *depression*, *physical inactivity*, *diabetes*, *limited social interaction*, *alcohol use*, *traumatic brain injury, and air pollution*.[6] AD is characterized by brain depositions of amyloid-β (Aβ) and tau proteins. Both Aβ and tau are debated as the underlying factors in developing AD pathology.[7] Tau pathology is linked to cognitive impairment and disease progression in AD.[8–10] However, in Parkinson's disease (PD) dementia, amyloid pathology may not be the primary driver of brain tissue atrophy and cognitive decline.[11] Alternatively, both Aβ and tau are likely to interact and contribute to AD development and progression; therefore, interventions directed towards both may be more effective than targeting them individually.[12]

There are currently no disease-modifying treatments (DMTs) that can stop AD from progressing once a diagnosis has been made or cure the condition. The lack of DMTs stems from the fact that we are unaware of the exact factors that trigger or contribute to AD development. Recent clinical trials demonstrated that lecanemab, aducanumab, and donenemab remove amyloid plaques and reduce cognitive deterioration in AD patients.[13–15] Further, two of these drugs, aducanumab in 2021 and lecanemab in 2023, were approved by the US Food and Drug Administration (FDA) for AD therapy.[16,17] Although not a cure, clearing the buildup of brain Aβ plaques is expected to slow the progression of cognitive impairment. All other drugs currently used in the clinic treat only the symptoms rather than target the factors that cause or progress AD.[3] Overall, there is a greater social, clinical, and economic demand for effective, accessible, and affordable DMTs to cure AD. One of the potential solutions for meeting this need is to repurpose approved generic drugs or clinical candidates with known pharmacokinetic, pharmacodynamic, and toxicity profiles.[18] Further, we have recently reviewed the different therapeutic approaches to NDDs, with the main conclusion suggesting that the use of some therapies in the early stages of the disease may have a beneficial effect.[19]

Several researchers have recently highlighted the growing interest in repurposing antineoplastic drugs for NDDs, given the lack of effective treatment for these disorders.[20–23] Researchers acknowledge that drug repurposing is a cost-effective, promising, and attractive strategy for AD drug discovery and development despite the limitations associated with antineoplastic therapy. Our review is focused mainly on AD and highlights the current status of research and development of new molecular entities or therapy, which remains poor despite significant investment and promising preclinical and clinical results. We focus not only on preclinical studies but also retrospective studies that indicate chemotherapy-treated cancer survivors have a reduced risk of Alzheimer's disease or dementia. We critically review both retrospective and preclinical studies to identify new areas for drug development, such as the prion-like spreading of pathologies. Lastly, we review major (current and past) clinical studies that have looked at the therapeutic potential of approved antineoplastics for AD patients with cognitive impairments and dementia of various severities. Reviewing these studies, we highlighted areas needing better clarification and presented extensive detail on these clinical trials.

2 | COMMON SHARED MECHANISMS BETWEEN CANCER AND AD

AD and cancer, traditionally viewed as distinct conditions, share surprising connections at the molecular level.[24–28] Both manifest aberrant cell cycle activity contributing to neurodegeneration, as noted by studies observing elevated cell cycle entry in AD.[29] This active cell cycle, characteristic of cancer pathogenesis, emerges as a crucial factor in both conditions.[29,30] The negative association between AD and cancer, highlighted in some research studies, implies a potential protective effect. Shared signaling pathways, such as p53, PIN1, BRCA1, and Wnt, and common risk factors like chronic inflammation underscore the intricate connection.[28,30] DNA damage accumulates in neurons and glial cells in AD, and genomic instability is a hallmark of cancer.[31] Shared pathways involve genes related to apoptosis and proliferation and DNA repair proteins, all of which are critical in maintaining genomic integrity in both conditions.[31,32]

Due to the complexity of the mechanisms and the extensive coverage by other researchers, it is beyond the scope of our study to delve comprehensively into each specific detail. However, our aim below is to draw readers' attention to two crucial alterations in both cancer and AD – altered proteostasis and metal dysregulation. These aspects have not been previously analyzed together, bringing the current attention to their significance.

2.1 | Altered proteostasis

Both cancer and NDDs involve disruptions in cellular proteostasis, such as in the ubiquitin-proteasome system (UPS) and autophagy. While enhanced UPS activity is observed in many cancers due to an increased protein turnover and a hostile tumor microenvironment,[33] impaired UPS function contributes to the accumulation of misfolded proteins in NDDs.[34] Defective autophagy, a common feature in both cancer and neurodegeneration, results in compromised clearance of protein aggregates in NDDs.[34]

Shared molecular players in autophagy, such as mammalian targets of rapamycin (mTOR) and Beclin-1, a tumor suppressor protein that is reduced in AD brains,[35] may contribute to the observed relationship. Further, tumor suppressor p53 and oncogene c-Myc are involved in regulating proteostasis,[33,36] particularly the MYC-p19^{ARF}-MDM2-p53 tumor-suppressive pathway modulates proteostasis through the regulation of autophagy. Experimental evidence has indicated the dual role of p53 in autophagy regulation, influenced by its subcellular localization and mode of action; notably, p53 deficiency or the accumulation of mutant variants in tumor cell cytoplasm can activate autophagy.[37,38] Similarly, p62/SQSTM1 and NRF2 have dual roles in both tumor and NDDs. The cellular context, stage of disease, and specific microenvironment influence whether p62 acts as a tumor suppressor or promoter or as a neuroprotective or pathogenic factor.[39–42]

Amyloid precursor protein (APP) and tau play crucial roles in the pathogenesis of AD, with emerging connections to cancer.[43] Aberrant processing of APP in AD is associated with the generation of toxic Aβ peptides. Caspase-mediated cleavage of tau contributes to neurofibrillary tangles (NFT) formation in AD.[44] At the same time, similar processes are implicated in cell survival and metastasis in certain cancers, such as APP cleavage in non-luminal breast cancers[45] and tau in neuroblastoma cells,[46] highlighting shared vulnerabilities that impact both neurodegeneration and cancer progression.

2.2 | Metal dysregulation in cancer and AD

Metal ions play pivotal roles in both cancer and AD, contributing to the intricate interplay between these seemingly disparate conditions (Table 1). Metal ions like iron, manganese, copper, zinc, and calcium have a crucial role in maintaining normal brain physiological functions.[52,53] The dysregulation of divalent and trivalent metal ions in different stages of AD leads to a sequential buildup of metals during disease progression, resulting in oxidative stress, activation of key enzymes and pathways involved in Aβ overproduction, and tau hyperphosphorylation leading to downstream neurotoxic effects, ultimately contributing to the neurodegeneration seen in AD.[54,55]

Zinc acts as a regulator of DNA repair mechanisms and apoptosis, with dysregulated zinc homeostasis in cancer cells often leading to impaired DNA repair and evasion of apoptosis, promoting uncontrolled cell growth.[56] Altered expression of zinc transporter proteins, ZIP and ZnT, is a common theme across various malignancies.[57] There is a causal link between increased circulating zinc and high-grade serous subtypes of ovarian cancer in women.[58] In AD brains, abnormal zinc levels have been noted, and these levels elevate in tissues where there is an accumulation of Aβ.[59] Postmortem analyses of AD amyloid plaques showed higher levels of zinc compared to normal (3.1 times more zinc).[60] However, synaptic zinc(II) sequestration by Aβ oligomers causes synaptic loss in hippocampal neurons.[60] Apart from AD, a rodent study indicates that prenatal zinc deficiency may also be linked to autism spectrum disorder.[61]

Copper is an essential micronutrient needed for several biological functions that affect overall health.[60,62,63] It is another important trace element that is deregulated in both cancer and AD. Elevated copper levels and copper/zinc ratio imbalances are associated with worse survival outcomes for hepatocellular and thyroid carcinomas.[64,65] Furthermore, prospective cohort studies on acute myeloid leukemia underscore the potential of copper and zinc levels as predictive biomarkers,[66] providing a comprehensive understanding of their roles in diverse cancer types. In the brain, copper is essential for different physiological functions of neurons[60]; however, enzyme-unbound free copper results in toxicity due to redox activity, pathologically affecting protein, lipids, and nucleic acids in different NDDs, including AD.[67] Distinct alterations in copper levels are also observed in AD and type-2 diabetes mellitus, suggesting a potential link between copper-induced toxicity and the intricate interplay between these diseases.[63] Further, copper(II) ions are suggested to interact with Aβ, promoting Aβ aggregation into non-fibrillar, amorphous aggregates.[68] Post-mortem analyses of AD amyloid plaques indicated a 5.7-fold increase in copper levels compared to normal brains, suggesting a potential link to AD pathogenesis.[60]

TABLE 1 Summary of metal ion roles in cancer and AD.

Metal ion	Cancer role	AD role	Dysregulation effects	Therapeutic Implications for AD	References
Iron	✓	✓	Oxidative stress, Aβ aggregation, tau accumulation	✓ Metal chelation therapy	[47]
Zinc	✓	✓	Impaired DNA repair, synaptic loss	✓ Metal chelators, zinc modulation	[48, 49]
Copper	✓	✓	Worse survival outcomes, Aβ aggregation	✓ Metal chelators, copper modulation	[50, 51]

Iron is a redox-active micronutrient that plays a dual role in the contexts of cancer and AD, with its dysregulation contributing to pathological processes in both conditions. In cancer, dysregulated iron homeostasis is a common phenomenon observed across various malignancies.[69] Iron is an essential cofactor for enzymes involved in DNA synthesis and repair.[70] Ovarian cancer cells exhibit altered iron metabolism, leading to increased cellular proliferation and survival.[71] Iron overload in cancer cells contributes to oxidative stress and DNA damage, promoting neoplastic transformation.[70] This dysregulation of iron homeostasis is intricately linked to the aggressive nature of tumors, influencing their growth, invasion, and angiogenesis.[70,71] Iron is involved in key enzymatic and signaling pathways in the brain, and its imbalance contributes to oxidative stress, a hallmark of AD.[72] Iron in amyloid plaques of AD brains is 2.8 times higher than those from normal brains,[60] again linking iron dysregulation to neurodegenerative processes in AD. Iron(III) resulted in distinct aggregation properties of Aβ, leading to the formation of annular protofibrils and fibrillar oligomers of Aβ.[73] Moreover, tau accumulation has been found to induce iron deposition, creating a toxic cycle that leads to synaptic deficits and memory impairment.[47]

The use of metal chelators to modulate radical formation and pro-inflammatory response may be useful in both diseases.[50] Even though metal ions have been associated with inflammation and cell death, a distinct role in both processes has not been established. The suitability of metal chelation therapy for treating NDDs is a subject of controversy,[52] attributed to various factors, including the delicate balance required for maintaining metal homeostasis in both health and disease. This complexity is exemplified by the dual nature of copper's behavior.[63] Further, the variations in research on the role of different metals in AD pathogenies also pose challenges in the strategic identification of metal ions for targeting.[53] There is a need for additional investigations, especially in understanding the dynamics of metals in AD patients, including their correlation with cerebrospinal fluid (CSF) biomarkers.[53] Nonetheless, there is a consistency among different studies that link decreased zinc and increased copper levels in AD patients.[53] Hence, modulation of deregulated metal homeostasis or developing new compounds (chelators) that can bind to metal ions, like clioquinol, PBT-2, metformin, and cyclodipeptides, could be potential avenues for exploring alternative treatments for AD.[47-51,55,74]

3 | DRUG REPURPOSING

While not a novel approach, dating back several decades, drug repurposing has gained popularity in recent years due to a faster and more cost-effective pathway for drug development.[18,75] More than 30% of marketed drugs and vaccines approved by the FDA have undergone a drug repurposing strategy.[75–77] Drug repurposing involves primarily two-on-target and off-target -strategies that use theoretical/in silico-based/computational and activity-based/biological experimental approaches or a mix of both.[78–82] These strategies have been comprehensively covered in several recent publications, and readers may benefit from these references [[78–82]]. In terms of NDDs, drug repurposing predominantly involves retrospective clinical analysis, ad hoc evaluation of clinical and epidemiological risks in human trials, and preclinical investigations using rodent models.[80]

3.1 | Computer-aided drug design and artificial intelligence

Computer-aided drug design (CADD) is transforming CNS drug discovery, leveraging algorithms for predicting molecule activity and identifying potential candidates through methods like pharmacophore modeling and molecular docking.[83] Incorporating artificial intelligence (AI) and machine learning is proposed to enhance drug repurposing, offering improved cost-efficiency, speed, and precision.[84] Notably, studies across various diseases have leveraged AI to identify novel repurposing candidates. AI analysis identified metformin and escitalopram as potential cardiovascular disease drugs.[85] In ALS, AL was used to develop a machine-learning model using voice and accelerometer data to measure disease severity.[86] Similarly, for Huntington's disease (HD), virtual screening and

computational analysis predicted FDA-approved drugs' interaction with the sigma-1 receptor, showing promise for HD treatment.[87] In AD research,[88] antibiotic development,[89] and COVID-19,[90] AI technology rapidly identified potential drugs and optimized treatment strategies. Flavonoids, alkaloids, and xanthones inhibit key enzymes in NDDs. Combining this knowledge with virtual screening methods revealed promising compounds from the Apocynaceae family that are relevant for AD and PD.[91] In cancer research, a novel approach called KUALA (Kinase drUgs mAchine Learning framework) utilized AI to automatically identify kinase active ligands for effective drug repositioning within the protein kinase family.[92] AI is not limited to ligand identification, but it can help identify molecular targets. For example, PandaOmics, an AI platform, was used to identify 11 novel therapeutic targets for ALS from CNS and iPSC-derived motor neuron data.[93] Validation of identified genes, KCNB2 and NR3C1, in an ALS Drosophila model, showed the promise of these targets in rescuing cells from neurodegeneration. This ALS study highlights the potential of using CADD and AI for drug repurposing, offering cost-effective and accelerated discovery methods with the ability to screen large datasets. However, it also emphasizes the essential requirement for thorough experimental validation to integrate computational findings effectively into biological systems.

3.2 | Drug repurposing–classic success stories

Many cases of successfully repurposing drugs have been recorded, showcasing their efficacy in addressing diverse health conditions. When we mention the "successful repositioning of drugs," we specifically refer to drugs that have obtained approval from drug regulatory agencies for human use. Some of the classic cases include that of thalidomide, sildenafil, minoxidil, zidovudine, and galantamine. (1) Thalidomide was introduced as an antiemetic drug in the 1950s but found new use as an effective treatment for erythema nodosum leprosum in 1998 and multiple myeloma in 2009 through off-label usage and pharmacological analysis approach of drug repurposing.[79,81] (2) Sildenafil was developed as an antihypertensive drug, but later, in 1998, it was repurposed as Viagra by Pfizer for treating erectile dysfunction through retrospective clinical analysis.[94] (3) Minoxidil was initially developed for hypertension, but later, in 1998, it was marketed as Rogaine by Pharmacia & Upjohn (currently Pfizer) for treating androgenetic alopecia through retrospective clinical analysis.[75,79] (4) Zidovudine was also another drug that was initially developed for cancers but later, in 1987, found use as the first anti-retroviral therapy for HIV/AIDS through an experimental approach of drug repurposing that involved in vitro screening compound libraries. (5) Lastly, galantamine, the anti-AD drug, was originally marketed as Nivalin by Sopharma for paralytic and neuropathic conditions, and its use was limited only to Bulgaria, Italy, France, and Germany during the 1960s through the 1980s.[95] But later, in 2001, due to its anticholinergic activity, it was approved for treating AD through mechanism-based drug repurposing. It is the only drug among the currently approved AD drugs that was developed through drug repurposing.

Recently, remdesivir, originally developed for hepatitis C and which underwent an unsuccessful Ebola trial in 2016, received approval from the FDA for treating COVID-19.[76,79,96–98] There are several other examples of non-neurological, neurological, and antidepressant drugs that have been successfully repurposed for new indications from their original indication, such as aspirin, atomoxetine, bupropion, chlorpromazine, duloxetine, eflornithine, finasteride, fluoxetine, ketoconazole, mifepristone, milacipran, raloxifene, ropinirole, sibutramine, and others.[75,76,79,81,96,99] More information on the successful repurposing of these and other drugs has been covered extensively by different authors in several comprehensive reviews (see refs. [75, 76, 79, 81, 96, 99] for further reading).

4 | CURRENT STATE OF R & D OF AD DRUGS

Currently approved pharmacological treatments for AD include memantine, an NMDA-receptor antagonist, for moderate-to-severe AD cases, and cholinesterase inhibitors (ChEIs), such as donepezil, galantamine, and rivastigmine for individuals with mild-to-moderate AD.[100–103] Additionally, in 2014, the FDA approved a combined

encapsulated form of memantine and donepezil, Namzaric®, for treating moderate-to-severe AD cases.[104] The ChEIs may also be used for treating Lewy body dementia (LBD) and vascular dementia if patients show comorbidity with AD, PD, or LBD.[105] The ChEIs and memantine have only modest effects in improving cognitive functions and the patients' quality of life. Interestingly, in AD mouse models, rivastigmine does not decrease the transcription of MYD88, a critical protein in Toll-like receptor signaling, suggesting that this therapy does not reduce neuroinflammation and, therefore, has a limited effect on cognitive impairment.[106] The overall clinical benefits of ChEIs at population levels are reportedly negligible, which resulted in the controversial removal of state funding for these drugs in France in 2018.[107]

The approved aducanumab and lecanemab are human-derived monoclonal Aβ antibodies that dose- and time-dependently reduce brain Aβ load in transgenic AD mice and prodromal or mild AD patients, slowing the decline in cognitive impairment.[108] Aducanumab targets oligomeric and fibrillar forms of Aβ but shows weaker interactions with Aβ monomers[109] and inhibits the secondary nucleation process in amyloid formation, a critical step in oligomer generation.[110] In double-blind and placebo-controlled Phase 3 trials, aducanumab at a higher dose was reported to reduce the clinical decline in cognition in AD patients aged 50–85 years, meeting the primary endpoint in one study but not in another.[13] However, despite the promising but not convincing clinical results, the 'accelerated approval' of aducanumab has generated more controversies in the scientific community and the pharma industry than its proposed therapeutic benefits for AD patients.[111–116] Similarly, lecanemab was reported to have reduced brain amyloid burden but moderately affected cognitive decline in early AD patients.[14] The drug resulted in mild-to-moderate infusion-related reactions in 24% and cerebral hemorrhages in 17.3% of study participants. Nonetheless, aducanumab and lecanemab are the only drugs approved after almost two decades since memantine approval in 2003.

Developing marketable new molecular entities (NMEs) is costly and uncertain. The average R&D cost for bringing NMEs into the market ranges from USD 161 million to USD 5 billion,[117] with the median prelaunch cost for the CNS ranging from USD 766 million.[118] The cumulative expenditure for R&D of AD drugs in the clinical stages from 1995 to 2021 was USD 5 billion, with the maximum cost incurred in Phase 3 trials.[119] Despite the significant investments, only six drugs - tacrine, donepezil, rivastigmine, galantamine, memantine, and aducanumab - have been licensed for AD treatment in the last 2.5 decades, with tacrine being discontinued in 2013 due to liver toxicity (Figure 1).[119] Besides the R&D costs, the lifetime treatment cost for a patient following diagnosis is estimated to be

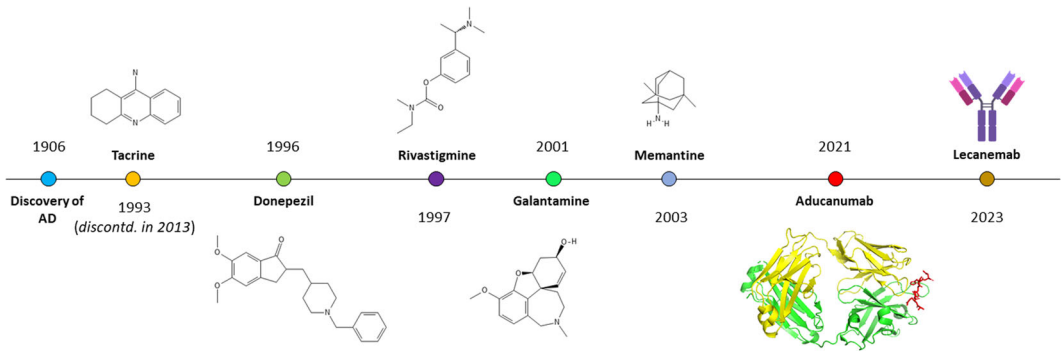

FIGURE 1 Timeline showing the Alzheimer's disease therapy. The structure of licensed drugs (Donepezil, Rivastigmine, Galantamine, Memantine, and Tacrine were obtained from PubChem and drawn using PubChem Sketcher V2.4. The antigen-binding region of Aducanumab (PDB ID: 6CO3) was drawn from the RCSB Protein data bank. The Aβ1-11 peptide of the Aducanumab-Aβ complex is depicted in red color. An Aβ-targeting Lecanemab (BAN2401), a humanized version of the mouse monoclonal antibody mAb158 sold under Leqembi, was approved by the FDA in January 2023 for the treatment of AD. A schematic depiction of IgG1 was created with BioRender. com. [Color figure can be viewed at wileyonlinelibrary.com]

more than USD 500,000.[120] The yearly maintenance dose cost of aducanumab is USD 28,200, which is relatively high for patients, particularly in low SDI countries.[115,121]

No significant progress has been made in developing new DMTs that target Aβ or tau deposits, except for the recent approval of aducanumab.[122,123] The lack of new DMTs is probably because of the relatively low approval rate of CNS drugs, which is less than that of non-CNS drugs in all phases of clinical trials, with the attrition of DMTs as high as 100%.[124–126] This low approval rate is linked to several factors, including the failure to show adequate efficacy and safety in Phase III trials and the poor understanding of the pathobiology of the target disease.[125]

Innovative drugs and new DMTs that the FDA has not approved in the clinic are needed to meet the need for aging-associated CNS diseases. However, developing new CNS drugs is lengthy and costly due to the need for regulatory approvals and uncertainty due to high drug attrition rates.[118,126,127] Repurposing existing drugs for CNS diseases will have several challenges, including commercialization issues, especially concerning generic drugs, and encountering intellectual property obstacles when considering patented drugs.[128] Nonetheless, repurposing FDA-approved generic drugs that have already undergone safety tests can substantially reduce the time and cost of drug development.[129]

A new innovative method involving machine learning called Drug Repurposing in AD (DRIAD) has been proposed to screen for new DMTs. For ranking the drugs as possible AD candidates, the association of DRIAD inputs from a list of mRNA expression profiles from brains at different stages of AD pathology was compared with a data set of drug-associated lists of genes that were differentially expressed when neuronal cells were exposed to the drugs. A combination of 80 FDA-approved or clinically tested drugs was then ranked for repurposing potential to increase the chance of successful hits.[130] Focusing on kinases, the JAK, ULK, and NEK families gave the highest scores in the ranking process. Another recent proposal for repurposing involved an *in silico* approach based on combining genomics, transcriptomics, and metabolomics.[131] Similar to DRIAD, antineoplastic for potential repurposing was associated with AD-related genes. Fifteen AD risk/protein-protein interaction genes were linked with 30 approved oncology drugs, from which four repurposing lead candidates were selected, three of which were epidermal growth factor receptor (EGFR) inhibitors.

5 | REDUCED RISK OF AD DEMENTIA AFTER ANTINEOPLASTICS USE–SUPPORTING EVIDENCE FOR REPURPOSING

5.1 | Evidence from retrospective cohort studies

Studies indicate that cancer survivors or individuals with a history of cancer have a lower risk of developing dementia or AD than individuals without cancer.[132–138] The inverse correlation has been noted for most cancers, but not all cancers, and between cancer and AD dementia. However, no association exists between cancer and non-AD dementia or cancer and other diseases such as stroke, osteoarthritis, and macular degeneration.[136,139] The reduced risk in cancer patients also appears to depend on age, gender, race, and cancer diagnosis time.[136] Whether this inverse correlation is due to biological and psychosocial mechanisms or pharmacological effects remains underexplored.[140–143] However, epidemiological studies indicate that patients receiving only chemotherapy had a reduced risk of AD diagnosis. Patients receiving only radiation treatment did not have a reduced risk of AD.[136] In patients over 65, chemotherapy reduced the risk of AD diagnosis by 21% and reduced the risk of dementia and other NDDs.[144] A similar inverse correlation between chemotherapy and AD risk was noted in Caucasian women diagnosed with breast cancer at ≥ 65 years.[143] A recent nationwide cohort study in Taiwan showed an increased risk of dementia in colorectal cancer (CRC) patients following chemotherapy, but only for patients over 80 years.[145] However, in this study, the non-chemotherapy group was composed of more patients over 80 years with a higher incidence rate of dementia. Nonetheless, the increased risk of dementia in CRC patients over 80 years is attributed to the susceptibility of the aging brain to chemotherapy-induced dementia due to aging-associated cerebrovascular and blood-brain barrier (BBB) defects.

The use of antihormone therapy has shown conflicting results in women and men. Female patients who received selective estrogen receptor modulators, such as tamoxifen or aromatase inhibitors, were diagnosed significantly less with AD and dementia.[146] Similarly, the long-term use of tamoxifen and aromatase inhibitors in postmenopausal women to treat breast cancer significantly lowered the risk of dementia.[147] However, antihormone therapy has generated conflicting results in men with prostate cancers. Androgen deprivation therapy in men increased the risk of non-AD dementia or cognitive defects but did not increase or decrease AD risk.[139,148,149] It is still unclear if the inverse correlation between chemotherapy and AD is specific to a type of cancer drug or if it is a general effect. However, more pronounced neuroprotection was observed with capecitabine, cetuximab, and panitumumab than with fluorouracil, oxaliplatin, and irinotecan in colorectal patients.[144] Panitumumab and cetuximab are inhibitors of EGFRs, making these receptors a potential target for AD therapy.[150]

There is general consent that neuroinflammation has a critical role in AD development and progression; therefore, treating central or peripheral inflammation may benefit AD patients.[19] The antineoplastic drug methotrexate is commonly used to treat autoimmune and inflammatory diseases. Even though methotrexate does not have a good profile for CNS diseases, chronic use in rheumatoid arthritis at a therapeutic dose different from antineoplastic therapy was shown to be protective against dementia more than another anti-rheumatoid drug, sulfasalazine.[151–153]

5.2 | Evidence of neuroprotective effects of antineoplastics in AD preclinical models

5.2.1 | Microtubule stabilization rescue from neurodegeneration

Because tau was generally accepted as a microtubule-stabilizing protein, drugs that stabilize microtubules, such as paclitaxel, epothilone B and D, peloruside A, and triazolopyrimidines, have been under investigation as potential AD treatments.[154,155] These studies with microtubule-stabilizing drugs (MSDs) attempted to restore the damaged microtubule network or ameliorate microtubule-associated functions to promote spatial memory and axonal recovery (Figure 2).[154,156] The protective effects of MSDs are not limited to AD but also show efficacy against PD[157,158] and multiple sclerosis.[159] However, it is uncertain whether the neuroprotective benefits of MSDs result from the amelioration of instability of brain microtubules.[156]

Despite the promising results from nearly two decades of studies with MSDs in transgenic animal models of AD, only a small number of drugs have progressed to clinical trials with AD patients since the end of the Phase 1 trial of epothilone D.[160] The most recent trials with an MSD for AD, corticobasal syndrome, and progressive supranuclear palsy patients were completed with abeotaxane (TPI-287), a brain-penetrant synthetic derivative of taxane. However, the outcome revealed no significant therapeutic benefits.[161]

Most investigations with MSDs are based on the presumption that pathological phosphorylation of tau causes it to lose microtubule stabilizing functions, resulting in neuronal microtubule breakdown and neurodegeneration (Figure 2). However, the work from the laboratory of Dr Peter Baas at Drexel University College of Medicine has challenged the generally recognized microtubule-stabilizing role of tau in neurons and, thus, the rationale for using microtubule-stabilizing drugs for NDD therapy.[162] His group has shown that tau does not stabilize the neuronal microtubules but allows them to grow and remain dynamic. It is known that taxanes or other MSDs have adverse side effects and may over-stabilize microtubules even in the low nanomolar range. Recent research findings indicate that selective estrogen receptor modulators, exemplified by tamoxifen and raloxifene, possess the capacity to influence microtubule stability, likely through their interaction with the taxane-binding site.[163]

Further, tamoxifen may also alter the phosphorylation of tau by inhibiting CDK5.[164] Therefore, microtubule-targeting drugs that do not over-stabilize microtubules and lead to retention of their dynamic properties may be better for recovering the damaged microtubules in AD brains. None of the observational studies, particularly those with breast cancer patients, mention any association between MSDs and AD, but a clear association between

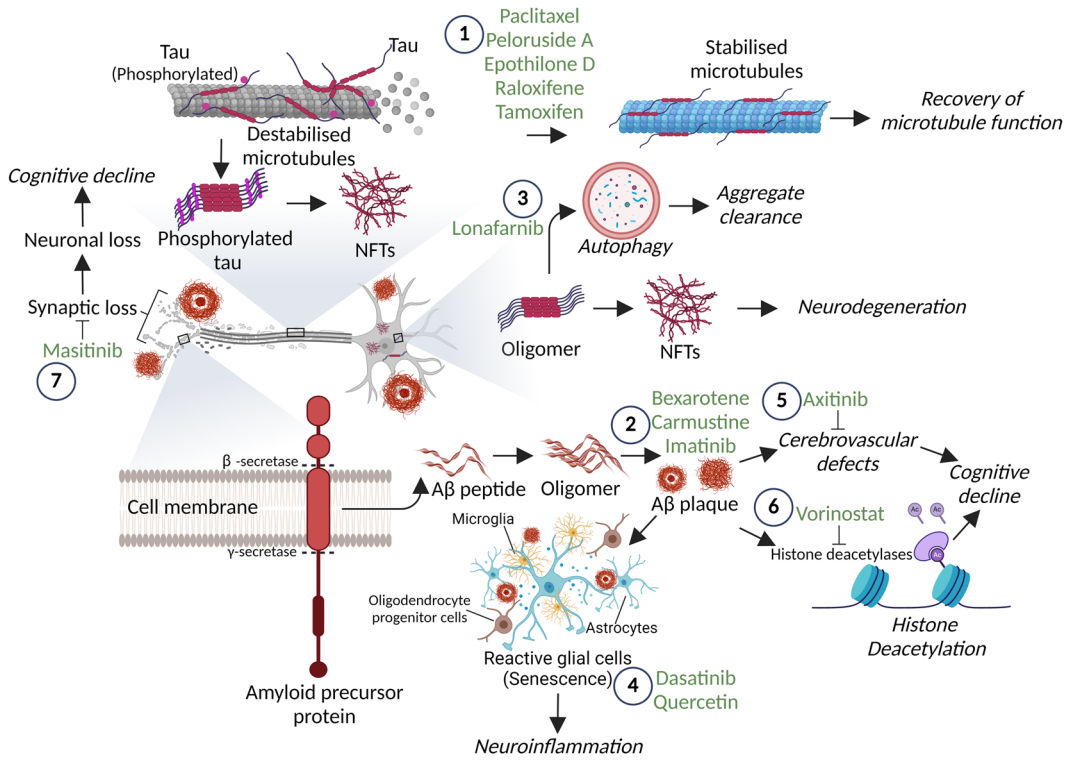

FIGURE 2 Schematic diagram showing the mechanism of neuroprotective effects of antineoplastics in AD preclinical models. (1) Paclitaxel, peloruside A, epothilone D, and tamoxifen restore microtubule stability and dynamicity, resulting in the recovery of microtubule functions. (2) Aβ-targeting drugs (bexarotene, carmustine, and imatinib) reduce the burden of Aβ plaques, reversing cognitive deficits. (3) Autophagy inducer lonafarnib-induced lysosomal clearance of tau pathology restores cognitive functions. (4) Extracellular Aβ plaques activate glial cells and induce senescence-like characteristics. Clearing senescent cells using senolytics (dasatinib and quercetin) reduces neuroinflammation, Aβ pathology, and cognitive deficits. (5) Axitinib modulates aberrant angiogenesis and corrects cerebrovascular defects. (6) HDAC inhibitor vorinostat restores epigenetic balance and reverses memory impairment. (7) Masitinib rescue of synaptic loss prevents cognitive decline. Created with BioRender. com. [Color figure can be viewed at wileyonlinelibrary.com]

tamoxifen and AD does exist.[146,147] Whether the long-term use of tamoxifen-corrected microtubule deficits restores key neuronal functions, synaptic plasticity, and cognition needs to be further examined.

5.2.2 | Reducing aggregated protein load and rescuing synaptic loss improve cognition

Defects in misfolded protein clearance mechanisms that act as the first line of cellular defense are prominent in cells with accumulated proteins or storage diseases.[165] Lonafarnib is an inhibitor of farnesyl transferase, an approved therapy for Hutchinson-Gilford progeria syndrome, in which an abnormal lamin A protein (progerin) accumulates in the cells. Lonafarnib is under investigation for cancer therapy and chronic delta hepatitis (NCT05229991; NCT00102648).[166] Autophagy induction is one of the pharmacological effects of lonafarnib (Figure 2). The compound activates lysosome-mediated clearance of tau pathology and, subsequently, reduces behavioral abnormalities in AD mice.[167] The downstream inhibition of mTOR by lonafarnib clears brain deposits of tau and restores cognitive functions in animals following ovariectomy with chronic administration of D-galactose.[168] However, once a significant

tau pathology has been set, it is possibly more challenging to clear tau tangles through autophagy induction, as evident from the fact that lonafarnib could not reverse existing pathology in rTg4510 transgenic mice.[167]

In another study, bexarotene, an FDA-approved drug for T-cell lymphoma therapy, was reported to reduce Aβ pathology and reverse cognitive deficits in transgenic AD mice.[169,170] Two other antineoplastics with different biological targets, carmustine, and imatinib, were also shown to reduce Aβ loads in AD mice[171,172] and Aβ production in amyloid precursor protein (APP)-expressing N2a cells and guinea pig brain (Figure 2).[173] The effects of imatinib were independent of BCR-Abl kinase and resulted, including that of carmustine, from the inhibition of γ-secretase cleavage of APP to toxic Aβ.[173] Apart from inhibiting Aβ, carmustine also disintegrates $Aβ_{42}$ protofibrils.[174]

Sunitinib is an FDA-approved drug for treating gastrointestinal stromal tumors and renal cell carcinoma resistant to imatinib and is in trials for treating neuroendocrine neoplasms.[175,176] Although it is a receptor tyrosine kinase inhibitor, its anti-acetylcholinesterase activity is proposed to attenuate cognitive impairments in scopolamine-treated mice.[177] Scopolamine is a nonspecific muscarinic receptor blocker. The neuroprotective effects of sunitinib are also associated with inhibiting the overproduction of nitric oxide in cellular models and may also result from inhibiting the activity of microtubule affinity-regulating kinase 4, a drug target for AD.[178–180]

Masitinib is a protein tyrosine kinase c-KIT inhibitor for treating mast cell tumors in dogs. The drug has shown promising results for AD in clinical trials and is under trial for potential use for amyotrophic lateral sclerosis (ALS) therapy.[181,182] It restored spatial memory in APPswe/PSEN1dE9 AD mice, possibly resulting from restoring synaptic functions since there was no reduction of either Aβ loads or neuroinflammation (Figure 2).[183]

In a recent phase 3 trial, the potential benefits of masitinib as an adjunct to existing treatments for mild-to-moderate dementia in probable AD patients were investigated.[184] Masitinib at 4.5 mg/kg/day led to significant cognitive and functional improvements compared to a placebo, suggesting potential efficacy.

Similar to the masitinib study, rescuing synaptic loss corrected cognitive deficits in APP/PS1 AD mice following treatment with saracatinib, an inhibitor of FYN and SRC-ABL.[185] FYN possibly inhibits Aβ-induced Fyn signaling-mediated hyperphosphorylation of tau. These studies show that therapies developed to target secondary pathways or proteins that affect the pathogenicity of primary AD proteins, Aβ, and tau, may provide a better rationale for repurposing anticancer drugs.

5.2.3 | Clearing senescent cells prevents neurodegeneration

Aging-associated accumulation of senescent cells contributes to the development of a range of human diseases.[186–188] Astrocytes and microglia obtained from mouse models of AD and frontotemporal dementia and postmortem brains of AD and PD patients display characteristic features of senescence.[189–193] Aβ aggregates induce a senescence-like phenotype in oligodendrocyte progenitor cells, and these senescent cells localize close to Aβ plaques.[194] Similarly, brain endothelial cells exposed to Aβ oligomers start displaying senescence-like characteristics with upregulated levels of VEGFR-1, which, when overexpressed in endothelial cells, results in senescence induction.[195] Whether VEGFR-targeting antineoplastic can disrupt the Aβ-VEGFR-senescence axis and alleviate NDD pathology remains unexplored.

A study by Hickson et al. was the first to show that senolytics reduce senescent cells in humans.[196] Selective clearance of senescent oligodendrocyte progenitor cells using a combination of dasatinib and quercetin reduces neuroinflammation and Aβ pathology development (Figure 2), reducing cognitive deficits in APP/PS1 AD mice.[194] The effect of the therapy on cognition may be due to epigenetic alterations in neuronal cells, as evidenced in a study with aged rats that lacked senescent cell burden in brains but showed improvements in cognitive functions due to changes in histone H3 methylation in the hippocampus.[197] Other clinical trials have shown that the combination of dasatinib and quercetin selectively reduces senescent cell burden from adipose tissues in kidney diseases in diabetic patients and alleviates idiopathic pulmonary fibrosis.[196,198]

5.2.4 | Targeting cerebrovascular defects improves cognition

Cerebrovascular diseases are comorbidities of aging and increase the risk of dementia. Cerebrovascular remodeling has been noted in human AD brains, and this alteration is associated with early tau pathology.[199] BBB dysfunctions have also been reported in AD, PD, and other NDDs.[200] These dysfunctions can contribute to the development of brain neuroinflammation, leading to neurodegeneration. Moreover, brain hypervascularity in AD due to Aβ oligomers can disrupt cerebral microvasculature and the BBB.[201,202]

Furthermore, analysis of cytokines, p-Tau181, and $A\beta_{1-42}$ levels in the CSF and peripheral blood of AD patients with APOE-ε4 genotype revealed a correlation between BBB dysfunction, peripheral inflammation, and IL-6 levels.[203] Since remodeling of cerebral arteries may contribute to microvascular pathology in AD,[199] correcting aberrant vascularization may prevent or delay AD. Targeting aberrant angiogenesis with axitinib, without directly targeting Aβ, corrected cerebrovascular defects and cognitive deficits in AD mice.[204] Axitinib is a VEGFR-targeting, FDA-approved drug for renal cell carcinoma therapy and has been in trials for melanoma and colorectal cancer.[205,206] These compounds can target secondary defects in AD rather than primary targets like Aβ and tau (Figure 2).

5.2.5 | Restoring epigenetic balance to improve memory deficit

Histones are necessary regulators of neuronal plasticity.[207] Amyloid pathology causes alterations in histone acetylation in human AD brains. Impairment in histone acetylation pathways decreases plasticity genes in animal models.[208-210] Histone deacetylases (HDACs) are becoming promising targets for the R&D of novel AD drugs or the repurposing of antineoplastic HDAC inhibitors, given the association of HDAC with cognition.[211,212] The FDA has approved four HDAC inhibitors primarily for cancer therapy- vorinostat, belinostat, and romidepsin for T-cell lymphomas and panobinostat for myeloma.[213] Vorinostat, a pan-HDAC inhibitor, has been used in different transgenic models of AD, aging, and high-fat diet, where it has reversed memory impairment but did not reduce amyloid load (Figure 2).[208] When combined with tadalafil, vorinostat is administered at low doses to overcome the adverse effects of pan-inhibition of HDACs.[211] It is now suggested that specific inhibitors of HDAC2 are more likely to have better therapeutic outcomes than pan-HDAC inhibitors.[214]

6 | CLINICAL TRIALS OF APPROVED ANTINEOPLASTICS FOR TREATING AD

Many established antineoplastics have been investigated or are currently being studied in clinical trials for therapeutic effects on AD patients with cognitive impairments and dementia of various severities.[20] To date, the published results of these trials have been promising but controversial. Many of these studies were underpowered and needed to be better designed, and their positive results need to be confirmed. Below, we discuss the status of R&D of approved antineoplastics for AD therapy.

6.1 | Lenalidomide and thalidomide

Lenalidomide is an approved drug for treating multiple myeloma, lymphoma, and myelodysplastic syndromes.[215] It is structurally similar to thalidomide, an immunomodulatory agent with poor safety and tolerability in AD clinical trials.[216] Lenalidomide studies in preclinical AD models are lacking. However, it has demonstrated neuroprotective effects in mouse models of ALS, multiple system atrophy (MSA), and PD.[217–219] The

neuroprotection resulted from the changes in pro-inflammatory and anti-inflammatory cytokine levels. Lenalidomide was reported to induce motor and cognitive impairments in Creutzfeldt-Jakob disease patients, raising questions about its further development for NDD therapy.[220] A Phase 2 trial with lenalidomide has been underway since 2022. It aims to analyze brain amyloid loads and neurodegeneration before and after dosing in individuals with mild cognitive impairment due to AD.[221] As for thalidomide, a double-blinded, placebo-controlled Phase 2 trial in mild to moderate AD patients showed poor drug tolerability and no cognition improvement.[216] Another Phase 2/3 trial with thalidomide was initiated in 2010 by Banner Sun Health Research Institute; however, the results are unknown (NCT01094340).

Thalidomide and lenalidomide down-modulate IL-17 transcription and secretion. This cytokine is involved in neuroinflammation, neutrophil migration, neurodegeneration, and cognitive impairment.[222–224] Several authors have proposed using anti-IL-17 therapy with its activities related to decreased peripheral and neuroinflammation.[19] A detailed statistical analysis of patients who received anti-IL17 biological treatment for psoriasis is required to ascertain a possible role of the cytokine in AD or neurodegeneration.

6.2 | Vorinostat

Vorinostat is an inhibitor of class I, II, and IV histone deacetylases (HDACs) and was the first HDAC inhibitor approved for treating advanced cutaneous T-cell lymphoma.[225] It has a plasma half-life of 2 h and a 100-fold lower concentration in the brain than the plasma of treated animals.[226,227] It is also a potential drug candidate for Niemann-Pick Type C (NPC), an aging-associated lysosomal storage disorder. NPC is characterized by progressive neurodegeneration and symptoms such as ataxia, seizures, cognitive decline, and severe dementia, in addition to NFTs and Aβ accumulation similar to AD, possibly due to endosome/lysosome abnormalities.[228]

Vorinostat was in a Phase 1 trial for maximum tolerable dose determination in AD patients with mild symptoms (NCT03056495). This study was completed in March 2022, and the results are pending. Another Phase 1/2 study comprising 12 participants was conducted in 2016 to repurpose Vorinostat for NPC therapy (NCT02124083). This study did not include placebo controls; nonetheless, there was no mortality, but other serious adverse effects were recorded, such as vomiting, gastrointestinal disorders, fatigue, infections, nervous system disorders, and others.

6.3 | Sulforaphane

Sulforaphane is a secondary metabolite of glucoraphanin in cruciferous vegetables consumed by humans with antioxidant and anti-inflammatory activities.[229] Preclinical studies have shown that the anticancer activities of sulforaphane result from several mechanisms in multiple cancer models.[230] A number of preclinical studies have also reported the neuroprotective effects of sulforaphane against other NDDs. Cumulatively, these studies show that sulforaphane reduced tau and Aβ burden, inflammation, oxidative stress, and neurodegeneration.[229]

Sulforaphane ameliorated neurobehavioral deficits and Aβ burden in a mouse AD model by reducing the expression of HDAC1-3. Its inhibition reverses AD pathology although increasing neurotrophin receptor p75, which has been recently shown to contribute to Aβ oligomer-mediated toxicity.[231,232] Aβ oligomer binding to the neurotrophin receptor p75 triggers signaling cascades that cause dendritic spine pathology in hippocampal neurons.[233] How a sulforaphane-induced increase in neurotrophin receptor p75 levels will contribute to Aβ toxicity needs to be explored further.

There is only one ongoing human trial with sulforaphane done by The Second Affiliated Hospital, School of Medicine, Zhejiang University, which is recruiting AD candidates to evaluate its efficacy, safety, and mechanism of

action (NCT04213391). The drug is proposed to improve cognitive impairment by altering inflammation and oxidative stress.

Inhibition of NF-κB is critical in neuroinflammation. Sulforaphane is an excellent inhibitor of NF-κB signaling, MAPK, and AGE-RAGE signaling pathways in leukocytes and microglia.[234,235] Thus, this drug can be considered one of the most promising current therapies for AD.

6.4 | Dasatinib and quercetin

Dasatinib is an FDA-approved drug for treating acute lymphoblastic and chronic myelogenous leukemia (CML). The drug is highly effective in imatinib-resistant CML patients.[236,237] Quercetin has exhibited promising anticancer potential in experimental and preclinical studies.[238] However, further research is required to establish its optimal dose and ensure its efficacy and safety in clinical applications.[239] Experimental evidence suggests that quercetin may induce neuropathy at doses exceeding 4% and elevate cancer risk when its concentration exceeds five micromoles per liter.[240]

In the context of NDD, the combination of these senolytics has shown great promise in alleviating disease phenotypes in several preclinical studies with different AD models.[194] Dasatinib and quercetin effectively reduce senescent cells and inflammation in aging mice.[241,242] The combination therapy also reduced intestinal senescent cells and inflammation, indicating that the drugs might improve health by altering the gut microbiota signatures.[242] There is ample evidence to suggest that modulations in gut microbiota are a potential risk factor for AD and PD.[243,244] The gut-brain axis is mainly linked to the pathobiology of PD through intestinal inflammation,[245] and evidence shows that α-synuclein pathology originates in the enteric nervous system in the gut and spreads to the brain.[246]

A combination of dasatinib and quercetin is in a double-blinded placebo-controlled Phase 2 SToMP-AD trial as potential senolytic therapy for early-stage AD or with mild cognitive impairment patients (NCT04685590). The therapy safety, tolerability, and BBB permeability to reach therapeutically relevant concentrations in the brain are being investigated in a 12-week Phase 1/2 study in early-stage AD patients (NCT04063124).[247] The study is not placebo-controlled, and the participants are already under treatment with donepezil. The conversion of endogenous α-Synuclein to pathological aggregates in the central and gastrointestinal (enteric) nervous system is a common feature of PD. Since these two drugs may improve the imbalance of gut microbiota by reducing intestinal inflammation caused by a senescence-associated secretory phenotype,[246] further studies at preclinical and clinical levels are warranted to determine the feasibility of using them to treat PD.

6.5 | Daratumumab

Neuroinflammation is involved in AD and other NDDs like PD, ALS, and HD.[248] Even though each disease's conditions differ, the immune system's role in the disease is evident. The glycoprotein, CD38, expressed on the surface of different immune cells, increases with aging, and clinical data indicate an increase in CD38 + T-cells in the blood of AD patients in the early stages of the disease. Experimental data show that Aβ promotes CD38 expression in senescent microglia in APP/PS1 mouse brains, and inhibiting or knocking out CD38 reduces neuroinflammation and cognitive impairment.[249] Crossing an APPswePS1ΔE9 (AD-prone) mouse with a CD38 knockout mouse reduced Aβ pathology in AD-prone mice.[250] Following these findings, an anti-CD38 antibody, daratumumab, has been approved for treating multiple myeloma[251] and is currently in Phase 2 trials for treating mild to moderate AD patients (NCT04070378). Daratumumab has been successfully used in antibody-related neurological disorders, giving rise to its possible use in autoimmune diseases.[252]

6.6 | Nilotinib and masitinib

Nilotinib is a brain-penetrant oral Bcr-Abl tyrosine kinase inhibitor approved for treating individuals diagnosed with chronic myeloid leukemia.[253] Due to its effect on Bcr-Abl, nilotinib was shown to have neuroprotective activity in PD animal models and cleared tau deposits in P301L mice.[254,255] Several clinical trials with nilotinib were completed in AD, PD, and LBD patients,[256–260] generating mixed results. Some other studies are underway, with one study in the Phase 3 stage (NCT05143528).

Another selective tyrosine kinase inhibitor of c-kit, masitinib, is also being studied as a potential therapy for AD.[183] The drug is used for treating mast cell tumors in dogs and is under investigation for treating human cancers.[261] In a placebo-controlled Phase 2 trial, masitinib slowed cognitive decline in mild-to-moderate AD patients receiving ChEIs or memantine.[181] In another Phase 2b/3 study comprising 718 mild-to-moderate AD patients, masitinib reduced cognitive decline and progression to severe dementia.[262]

A relationship between peripheral blood immune markers, neuroinflammation, and neurodegenerative disorders was indicated.[263] The modulation of P38/STAT3 by nilotinib decreased cognitive decline after exposure to lipopolysaccharide, suggesting that this compound could reduce neuroinflammation in pathogen-induced peripheral inflammation.[264] However, nilotinib has been shown to block discoidin domain 2, increasing aortic calcification and coagulation.[265,266] Thus, nilotinib should not be used in ApoE-related neurodegeneration. Imatinib has a better profile since it reduces lesions in experimental models of multiple sclerosis.[267,268] Moreover, in a study analyzing molecular interactions, the chemical structures of ponatinib and niraparib were shown to have a dual effect as inhibitors of brain acetylcholinesterase.[269] Compounds with dual effects can be important for future drug design and open a logical paradigm with the current therapies used in cancer. More statistical meta-analysis is required to determine if this drug class decreases neuroinflammation.

6.7 | Tamibarotene

The synthetic retinoid tamibarotene is an approved drug for treating acute promyelocytic leukemia in Japan. It has also demonstrated anti-AD activity in preclinical models through microglia-mediated clearance of Aβ oligomers and targeting APP processing.[270,271] A Phase 2 study with tamibarotene was initiated in 2010, but the study outcome remains unpublished (NCT01120002). Tamibarone has been shown to modulate T-cell responses in several experimental models. The drug enhances neutrophil function and regulates IL17/Th17 responses associated with cell migration, neuroinflammation, and cognitive response.[272,273] The decrease in the peripheral inflammatory response and the downregulation of the IL17/IL23 axis is probably responsible for the benefits reported in the preclinical trials. However, the pharmacokinetics and pharmacodynamics of synthetic retinoids are complex. This complexity may account for the lack of data in clinical trials. Other synthetic retinoids may be better candidates for neurodegeneration.

6.8 | Nabilone

Nabilone is a synthetic cannabinoid approved to treat chemotherapy-related nausea in cancer patients who do not respond to other anti-emetics. It is a BBB-penetrant partial agonist of cannabinoid CB1 and CB2 receptors in the CNS. Nabilone has been in clinical trials to manage and treat agitation and aggression in advanced AD patients.[274–277] Cannabinoids have decreased local and peripheral inflammation.[278] The effect seems related to CB2 receptors that modulate microglial functions in AD mouse models.[279] Conversely, no significant benefits were observed in a small trial with dementia and a meta-analysis in neurological and oncological patients.[280,281] Although different cannabinoid receptors can be involved in the array of responses (positive and negative), more detailed

research is needed to ascertain the benefits of the therapy in systemic inflammation and neurodegenerative diseases.

6.9 | Lapatinib ditosylate

Lapatinib ditosylate is a dual tyrosine kinase inhibitor of epidermal growth factor receptor (HER2) and EGFR and is approved for treating advanced or metastasized breast cancer. It is often prescribed in combination with other antineoplastics, such as capecitabine or Letrozole, in women with HER2+ breast cancer. A recent study reported that lapatinib could improve cognitive impairment by modulating the PI3K/Akt/GSK-3β pathway and decrease Aβ aggregation via autophagy enhancement in D-galactose/ovariectomized rats. The treatment also reduced neuroinflammation and oxidative stress.[168] These correlation and convergent findings provide new biological insights into the potential therapeutic benefits of lapatinib in treating AD. Another study showed that chronic therapy with lapatinib reduced $A\beta_{1\text{-}42}$ and p-tau accumulation, improving cognitive impairment by modulating p-mTOR, ERR-α, P38-MAPK, and HER-2 in rats.[282] Additionally, lapatinib reduces excitotoxicity by inhibiting GluR-II, mitochondrial pyruvate carrier-1 (MPC-1), and neuroinflammation by inhibiting NOX-1 and TNF-α.[282] Based on these findings, lapatinib may represent a novel repurposing option for treating AD. Promising preclinical results give a way to perform clinical studies to see the efficacy of lapatinib for AD.

6.10 | Leuprolide

Leuprolide belongs to the gonadotropin-releasing hormone (GnRH) agonist class of medications and is FDA-approved for managing and treating advanced prostate cancer. Chronic leuprolide treatment downregulates the synthesis and secretion of follicle-stimulating hormone (FSH) and Luteinizing hormone (LH) by disrupting the pulsatile secretion of GnRH, thereby suppressing the circulatory gonadal sex hormones. It is commonly used to manage prostate cancer, assist in fertility treatments, alleviate severe endometriosis, reduce uterine fibroids, and treat precocious puberty in children. There is growing evidence to support the role of elevated gonadotropins in AD pathogenesis. Preclinical studies have shown that decreased levels of LH are linked to improved cognitive function and lower levels of both amyloid deposition and tau phosphorylation in different animal models of AD.[283–285] Clinical trials are ongoing to investigate leuprolide's safety and efficacy for treating AD. A 48-week study employing low-dose (11.25 mg leuprolide acetate) and high-dose (22.5 mg leuprolide acetate) injections given every 12 weeks under double-blinded, placebo-controlled conditions revealed no statistically significant variations in primary efficacy parameters (ADAS-Cog and ADCS-CGIC) or secondary efficacy parameters (NPI, ADCS-ADL, BI, and ADCS-Severity Rating).[286] A subgroup analysis of patients concurrently using a ChEI showed a significant benefit in the high-dose Lupron group.[286] The study findings suggest a positive interaction between Lupron and ChEIs, emphasizing the need for further investigation into this combination for Alzheimer's disease treatment. A Phase II trial is ongoing that is investigating the efficacy of a 48-week regimen of Leuprolide (22.5 mg per 12 weeks) compared to placebo on cognitive function, global function, and plasma and neuroimaging biomarkers (NCT03649724).[287]

6.11 | Temsirolimus

Temsirolimus is another FDA- and EMA-approved oncology drug for treating renal cell carcinoma. It belongs to a class of mTOR inhibitors and, thus, plays an essential role in the regulation of cell growth, proliferation, and survival. A study reported that the administration of temsirolimus improved the autophagic clearance of Aβ in both HEK293-

APP695 cells and the brains of APP/PS1 mice.[288] Furthermore, temsirolimus mitigated cellular apoptosis in APP/PS1 mice's hippocampus, enhancing spatial learning and memory abilities. Another preclinical study reported that rapamycin ester analog CCI-779/Temsirolimus decreased the brain levels of sarkosyl insoluble tau and phospho tau in Tg30 mutant mice. These findings suggest that temsirolimus administration may provide a novel therapeutic approach for treating AD. However, clinical studies are required to establish the above findings.

6.12 | Raloxifene

Raloxifene, a selective estrogen receptor modulator, is the only FDA-approved drug in the US to help lower the risk of breast cancer in postmenopausal women who have a high risk for developing the disease or who have osteoporosis. It activates the transmembrane G-protein-coupled estrogen receptor (GPER), preventing mild cognitive impairment and restoring cognition. The drug also safeguards against Aβ oligomers-induced neurotoxicity by modifying oxidative parameters and maintaining [Ca2+] homeostasis.[289,290] Few clinical studies have investigated raloxifene's safety and efficacy for treating AD. In a randomized, double-blinded, placebo-controlled trial, 42 patients were randomized to receive raloxifene or placebo. The ADAS-cog change scores did not differ significantly between treatment groups. Additionally, there was no difference in dementia rating, activities of daily living, behavior, or global cognition composite score.[291] Currently, no clinical trials are ongoing to investigate the efficacy of raloxifene on AD.

6.13 | Bosutinib

Bosutinib, a tyrosine kinase inhibitor, is employed for treating specific cancer types, notably CML and Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL). Its mechanism of action involves the inhibition of tyrosine kinases, enzymes crucial for the abnormal proliferation and division of cancer cells. Preclinical investigations of bosutinib reported elevated levels of IL-10 and CX3CL1 in the brain and blood. These findings imply that tyrosine kinase inhibitors (TKIs) regulate soluble CX3CL1 in the brain. However, this effect may be interconnected with systemic CX3CL1 levels in the initial stages of the disease.[263] Bosutinib could produce a synchronized impact by influencing a unified blood-brain immune response and facilitating the clearance of amyloidogenic proteins in neurodegeneration.[263] Another study suggests that bosutinib increases soluble parkin levels, leading to the clearance of amyloid and improved cognitive function.[292] These findings suggest the potential effects of bosutinib as an early-stage treatment for AD, offering anti-inflammatory and neurorestorative effects.

7 | CHALLENGES WITH REPURPOSING OF ANTINEOPLASTIC DRUGS

AD involves complex neurodegenerative processes (Figure 2), while antineoplastics are primarily designed to target cancer cells. The mechanisms of action for these drugs may not align with the intricate pathology of Alzheimer's, requiring careful consideration of how they may impact neural tissues. The potential side effects of these drugs, such as neurotoxicity and cognitive impairment, pose a significant concern, potentially exacerbating existing cognitive issues in AD patients. Chemo brain or cancer-related cognitive impairment (CRCI) is a well-recognized neurotoxicity associated with chemotherapy, which is linked to inflammation, oxidative stress, and disrupted neurogenesis.[293,294] The mechanisms behind chemo brain remain partially understood; however, studies indicate that chemo brain resulting from the use of cisplatin, oxaliplatin, and paclitaxel is related to sphingosine-1-phosphate (S1P) levels and the ceramide-to-S1P pathway in the brain.[295,296] S1P receptor 1 antagonists, such as FDA-approved multiple sclerosis drugs like ozanimod and fingolimod, have shown promise in mitigating CRCI by

modulating neuroinflammatory processes.[295,296] The imbalance between pro and anti-inflammatory cytokines contributing to depression symptoms in CRCI suggests that certain antidepressants could positively influence chemotherapy-induced inflammation and cognitive dysfunction by restoring cytokine balance.[293] Therefore, combining antineoplastics with approved drugs that mitigate CRCI may offer a potential strategy to address challenges in repurposing these drugs for AD.

The heterogeneity among AD patients adds another layer of complexity to drug repurposing efforts, necessitating tailored treatments for specific subtypes or stages of the disease. Another layer of complexity arises from 'polypharmacy' effects in older adults, which may complicate the use of antineoplastics, particularly in this age group.[297] This complexity is further heightened in patients with AD and dementia, where the aging process can alter physiological functions, impacting drug pharmacokinetics, pharmacodynamics, and tissue tolerance.[298,299] To navigate these challenges effectively, a comprehensive geriatric assessment (CGA) will be a valuable tool. CGA not only aids in identifying patients at risk of toxicity but also guides the selection of drugs and therapeutic strategies.[298,300] This is exemplified by documented instances of reduced drug toxicity in treatments guided by CGA.[301] However, a critical aspect of addressing these challenges lies in the inclusion of underrepresented older individuals in clinical trials.[300] Additionally, transparent reporting of both antineoplastic efficacy and toxicity is crucial for a comprehensive understanding.[300] Such insights are essential for the successful repurposing of antineoplastic drugs for age-related CNS disorders, particularly AD. A comprehensive analysis of anticancer studies indicates that cognitive decline observed after low-dose chemotherapy is temporary, while higher doses lead to prolonged effects posttreatment.[294] This empirical evidence underscores the need to strike a careful balance between therapeutic benefits and potential adverse effects in the repurposing of antineoplastic.

Apart from neurotoxicity, the BBB presents a challenge in delivering antineoplastic effectively to the brain due to the abundance of efflux transporters.[302] This challenge can be addressed with the use of nanocarriers,[303] such as liposomes, to deliver drugs across the BBB, as has been demonstrated for temozolomide and doxorubicin.[304] Further, new, improved delivery systems for targeted delivery of nanocarrier-loaded drugs into specific brain regions will be essential for repurposing antineoplastic.[305] Exploiting the emerging knowledge from the R&D of CNS anticancer drugs will help identify suitable BBB-penetrant candidates for NDDs. A preclinical study in brain metastasis models of mice demonstrated a better BBB permeability of osimertinib than EGFR inhibitors such as gefitinib, rociletinib, and afatinib.[306] Further, osimertinib also accumulated better in rat and cynomolgus monkey brains and showed improved clinical activity in human patients with brain metastases. The potential for osimertinib for NDD remains unexplored.

Overall, to tackle these challenges successfully, a comprehensive understanding of both AD's underlying mechanisms and the pharmacology of antineoplastic drugs is necessary. Collaborative efforts involving neuroscientists, oncologists, and drug developers are essential to navigate these complexities and optimize the potential benefits of repurposing antineoplastics for AD.

8 | PERSPECTIVES AND FUTURE DIRECTIONS

Different chemotherapeutics are used in the clinic to treat human cancers with multiple biological targets. So far, only limited clinical data are available on the type of antineoplastics that reduce AD risk. Drugs like fluorouracil, oxaliplatin, irinotecan, panitumumab, cetuximab, capecitabin, tamoxifen, and aromatase inhibitors are the only drugs that have been reported to reduce AD risk.[144,146] However, how antineoplastics with different biological targets result in a similar outcome, that is, AD risk reduction, when AD is a multifactorial disease, is still an open-ended question (Figure 2).

Whether confounding factors contributed to a decreased risk of AD in cancer patients needs more exploration to dissociate the effect of the chemotherapeutic drug and lifestyle changes. Reduced incidences of AD in cancer patients following chemotherapy may be independent of the treatment and more dependent on adherence to a

healthy lifestyle after a diagnosis of cancer or following the end of cancer treatment. A healthy lifestyle inversely correlates with mortality in cancer survivors and risk of cardiovascular disease and type 2 diabetes.[307–309] Furthermore, individuals who lead healthy lifestyles live longer and remain dementia-free for most of their lives.[310] Following cancer diagnosis and treatment, significant lifestyle changes include adherence to a healthy diet, the use of dietary supplements, increased physical activity, and interest in social interactions and relationships.[311–313] Increased social interactions and healthy lifestyle changes may reduce stress in survivors, resulting in lower AD risk, as high cortisol has been reported to contribute to AD development.[314]

From a biological perspective, it is known that clonal hematopoiesis, a premalignant condition, confers protection from dementia due to AD, and some anticancer drugs reduce AD risk in cancer survivors.[20] Further, AD is characterized by the prion-like intraneuronal spreading of misfolded aggregates of Aβ and tau. These aggregates can develop early in AD brains before the onset of major histopathological hallmarks. Prion-like spreading may partly explain why the disease prognosis differs between individuals.[315,316] Tau spreading also occurs in normal aging brains, although the spread rate may be slower in normal aging than in tauopathies.[316] The presence of tau pathology precedes prominent gray matter atrophy in human AD brains, suggesting tau is a critical inducer of neurodegeneration.[317,318] Drugs that abolish the generation of prion-like aggregates of Aβ and tau or reverse the prion-likeness of pre-existing aggregates may rescue neurons from propagating misfolded proteins and the eventual neuronal deficits that lead to AD development. In this context, two studies with bexarotene show that it selectively interferes with the primary nucleation of $A\beta_{42}$, an early event in the aggregation process. It prolongs the lag time of fibrillization.[319,320] This selective interference at the early stages of the aggregation process prevents the formation of toxic $A\beta_{42}$ species and prevents AD onset if administered at a presymptomatic stage.[319] Similarly, we recently showed that drugs like paclitaxel, doxorubicin, resveratrol, and quercetin that interact with the amyloid motif and cysteine residue in tau repeat 3 block its nucleation-dependent aggregation, abolishing the formation of toxic, pathological prion-like aggregates of tau.[321]

The concept of removal of a toxic burden of misfolded proteins is not new. Sequestering oligomers from human patients with tau-positive inclusions in brains is expected to abolish tau spreading, even after pathological tau deposition has begun.[322] Therefore, it can be speculated that neurodegeneration would be prevented by rescuing neurons containing misfolded propagating protein aggregates at the early stages of the disease.[323] In the context of the reduced risk of AD development in cancer patients, therefore, it is possible that the cancer patients' brains, who were presymptomatic AD patients, had pre-existing aggregates of Aβ and tau and that chemotherapy acted as 'prophylactics' against the spreading these prion-like aggregates. This hypothesis aligns with findings showing a reduced risk of AD or enhanced cognitive functions in nonsteroidal anti-inflammatory drug users, provided the use was before dementia onset in susceptible individuals.[324,325] Therefore, further studies are necessary to establish a clear link showing which types of antineoplastics reduce AD risk in cancer patients and if these cohorts are presymptomatic AD patients by monitoring established biomarkers.

Current therapeutic approaches for AD are solely symptomatic, necessitating a rethinking of the rationale for drug design, including repurposing approved drugs or clinical candidates with known toxicity profiles to meet in a timely fashion the growing demand for effective, accessible, and affordable drugs. Several experimental or approved antineoplastics have shown potential neuroprotective effects in preclinical studies and clinical trials. Thus, there is a growing interest in their use as potential therapies for AD and other CNS diseases (Supporting Information: Table S1). Despite mounting evidence from preclinical and retrospective studies showing the neuroprotective effects of antineoplastic drugs and the reduced risk of AD in cancer patients following chemotherapy, the mechanisms for the neuroprotective effects of most antineoplastics remain elusive. Compared to oncology drugs, fewer Phase I trials start for CNS drugs, and most fail in the later Phase 3 trials.[125] Developing drugs that cross the BBB or formulations that aid compounds to cross the BBB at relevant pharmacological concentrations will be promising for AD therapy.[357] As a group of basic and translational researchers and clinicians, we believe these shortcomings highlight the need to prioritize the translation of basic research and allocate substantial funding for preclinical translational investigations. New approaches for AD drug development are needed to tackle the attrition rate of drugs in late-stage clinical trials, such as focusing on the early stages of AD

well ahead of the development of major histopathological changes and using experimental animal models that more accurately reproduce the disease complexities.

In our recent correspondence, we emphasized the critical relationship between cancer, chemotherapy, and AD.[358] Therefore, clinical trials involving individuals in the age group of cancer survivors must take into consideration their cancer history and previous treatment regimens. This consideration is crucial in the interpretation of trial outcomes focused on the efficacy of biologics or other pharmaceutical interventions for AD treatment. By integrating a nuanced understanding of how cancer and its therapies could impact AD progression or response to treatment, researchers can conduct a more thorough analysis of trial results, potentially revealing personalized strategies for addressing AD within this specific demographic.

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CONFLICT OF INTEREST STATEMENT

All authors declare no conflicts of interest/competing interests.

DATA AVAILABILITY STATEMENT

Data sharing not applicable–no new data generated.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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