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A narrative review of aging-targeted mechanisms and interventions in Alzheimer's disease

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Abstract

Background & Objective: The biggest risk factor for Alzheimer's disease (AD) is aging, contributing to impaired clearance of tau and amyloid-beta (Aβ) proteins, microglial senescence, endoplasmic reticulum (ER) stress, lipid dysregulation, and excitotoxicity. This review investigates how aging speeds up the pathophysiology of AD and evaluates emerging geroscience-based interventions targeting biological aging mechanisms to delay or prevent cognitive decline. *Methods:* A narrative review of the literature from 2015 to 2025 was conducted, integrating longitudinal studies, meta-analyses, and preclinical models that examine the aging-AD interface. The MEDLINE, Embase, Cochrane, Google Scholar, and PubMed databases were searched using specifically related keywords, such as ageing, AD, AD pathology, anti-aging strategies, and AD therapies. *Results:* An initial search identified 320 publications. After screening for relevance and removing duplicates, 220 studies were excluded and 30 duplicates removed, leaving 72 eligible studies for synthesis in this narrative review. These included preclinical, clinical, and meta-analytic data examining aging mechanisms and geroscience-based interventions in Alzheimer's disease. Most of these studies discussed aging-related mechanisms—glymphatic dysfunction, APOE ε4-associated lipid transport impairment, BDNF depletion, and glutamate excitotoxicity—, and anti-ageing strategies such as lifestyle interventions (e.g., physical activity, sleep optimization, cognitive engagement) and medical and biological therapies for AD.
Conclusion: Targeting aging mechanisms offers a paradigm shift in AD prevention and treatment; however, multidisciplinary collaboration is essential to translate geroscience into clinical practice. The integration of lifestyle and pharmacological strategies may yield synergistic neuroprotective benefits. Future research should focus on integrated, multimodal interventions that combine lifestyle modification with pharmacological and biological therapies. Tailored approaches—based on genetic risk profiles (e.g., APOE status), comorbidities, and individual aging trajectories—may optimize clinical outcomes. To evaluate the long-term safety and effectiveness of innovative treatments like senolytics, epigenetic modulators, and stem cell-based therapies in older populations, extensive, longitudinal clinical trials are also required. Developments in biological age biomarkers, machine learning, and systems biology have the potential to improve risk assessment and therapy customization.

Keywords: Alzheimer's disease, aging, neuroinflammation, senolytics, epigenetics, stem cell therapy.

INTRODUCTION

Between 60% and 80% of dementia cases worldwide are caused by Alzheimer's disease (AD), making it the most prevalent type of dementia.[1] As of 2025, approximately 60 million people worldwide are affected by dementia, and by 2050, projections suggest a rise to nearly 210 million 2050.[2] Age is the strongest risk factor, with AD affecting nearly half of those aged > 85 years.[3] In both the United States and Europe, the prevalence of AD increases with age, from 0.85% among individuals aged 65–69 years to 44.35% in those aged over 95 years.[4]

In addition to aging, Figure 1 shows several other factors that contribute to AD risk, including female sex, genetic predisposition, low educational attainment, head injuries, and lifestyle-related behaviors such as a sedentary lifestyle, smoking, alcohol use, and obesity. These risk factors synergistically interact with aging to promote the development of AD.[5]

Despite years of research, the treatment of AD remains limited. This highlights the need for novel approaches that target the underlying pathophysiology. The biggest risk factor for

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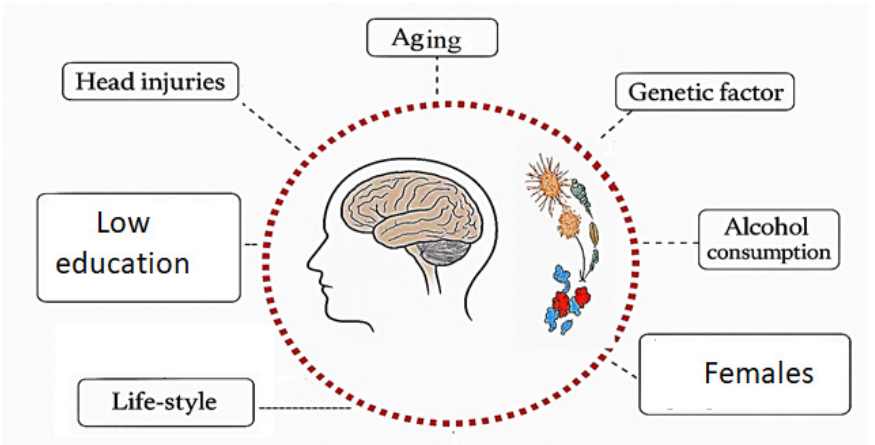

Figure 1. Risk factors of Alzheimer's disease

AD is aging, and targeting aging processes may be more successful than Aβ/p-tau strategies in altering the course of AD. This review critically evaluates the biological pathways through which aging contributes to AD pathogenesis and examines innovative lifestyle and pharmacological interventions that target these processes.

METHODS

This review followed a narrative integrative approach. Databases (PubMed, Embase, Cochrane, MEDLINE, and Google Scholar) were searched for studies published between 2015 and 2025 using keywords related to aging, Alzheimer's disease, and anti-aging interventions. Both human and preclinical studies were included to capture mechanistic and translational insights. Data were synthesized thematically into biological mechanisms, lifestyle interventions, and emerging biological therapies to ensure a coherent framework aligned with geroscience principles.

AGING MECHANISMS DRIVING ALZHEIMER'S PATHOLOGY

Aging induces systemic biological changes that disrupt homeostasis at the molecular, cellular, and tissue levels. These alterations include mitochondrial dysfunction, impaired proteostasis, genomic instability, oxidative stress, inflammation, and reduced regenerative capacity. In the brain, aging disrupts proteostasis, synaptic function, immune surveillance, metabolism, and the blood-brain barrier's (BBB) integrity.[3] The formation and clearance of amyloid-beta (Aβ) and phosphorylated tau (p-tau), neurotransmitter synthesis and release, microglial and astrocyte responses, neuronal excitability and plasticity, gut microbiota functions, and autophagy are all rapidly disrupted by these age-related changes—including oxidative stress, mitochondrial dysfunction, and blood-brain barrier breakdown—disrupt protein clearance, synaptic function, and immune regulation, ultimately driving AD progression[4], as shown in Figure 2.

Aβ/p-tau clearance and the glymphatic system

Aβ A is an acquired biomarker that can be used to predict disease because it appears a long time before the clinical signs of AD.[6] Under normal physiological conditions, Aβ is produced by neurons and efficiently removed via the glymphatic flow during sleep.[7] At normal levels, Aβ has numerous vital functions, including neuroprotection, memory improvement, and neuronal growth and repair. The accumulation of Aβ plaques is due to an imbalance between production and clearance. Its accumulation activates immune responses, causing neuronal destruction and memory impairment.[6] p-tau interacts with Aβ, exacerbating neurodegeneration through processes such as hyperphosphorylation.[7]

With advancing age, several structural and functional changes compromise the glymphatic efficiency. These include reduced aquaporin-4 (AQP4) polarization, diminished arterial pulsatility, and impaired cerebrospinal fluid and interstitial fluid exchange. Consequently, aged brains exhibit reduced clearance of Aβ, facilitating its aggregation into extracellular plaques, which is a defining feature of early AD pathology.[8]

Experimental evidence from aged rodent models and human neuroimaging studies has demonstrated a significant decline in glymphatic

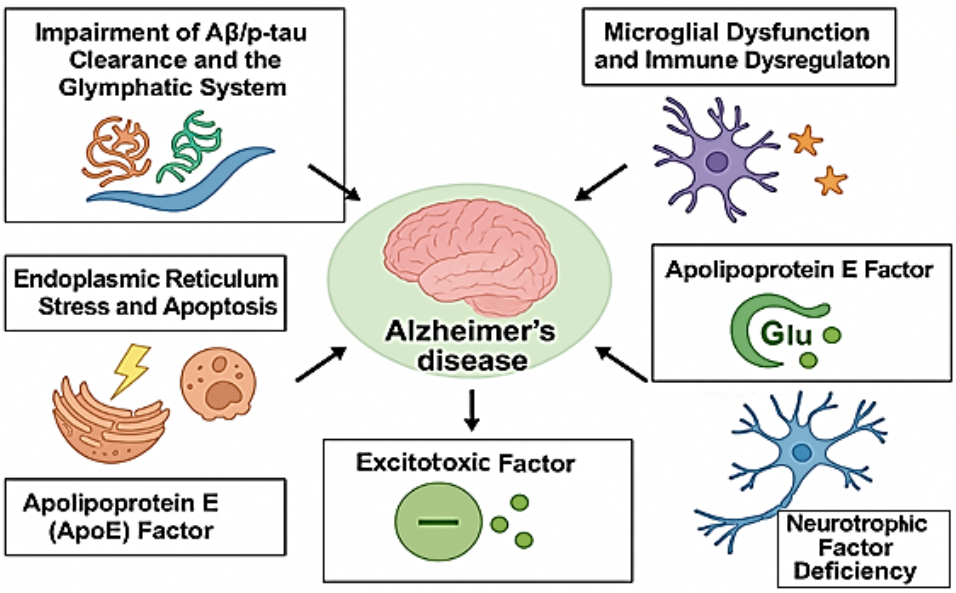

Figure 2. Pathology of Alzheimer's disease

clearance, which correlates with an increased Aβ burden. Interventions that improve sleep architecture, enhance vascular function, or stimulate AQP4 expression are being explored as therapeutic strategies to restore the glymphatic function and slow AD progression.[6]

Microglial and immune dysregulation

The brain's macrophages, known as microglia, are essential for preserving the homeostasis of the central nervous system because they monitor the surroundings, control inflammatory reactions, remove debris, including Aβ, and promote synaptic plasticity.[9]

However, with aging, microglia undergo functional decline, shifting from a neuroprotective to a pro-inflammatory state due to transcriptional changes that upregulate inflammatory genes while downregulating homeostatic genes.[10] This dysfunction is exacerbated by reduced phagocytic efficiency, which impairs the clearance of Aβ and contributes to plaque accumulation, neurotoxicity, and tau pathology.[8]

At the same time, pro-inflammatory cytokines such as interleukin-1 (IL-1β), IL-6, tumor necrosis factor-α, and -γ are elevated due to systemic immunological dysregulation in aging, which impairs memory formation, synaptic integrity, and neuronal function.[11] Central to this process is the transcription factor nuclear factor κB (NF-κB), which is activated by oxidative stress, mitochondrial dysfunction, and cellular senescence, which perpetuates inflammatory signaling. Together, microglial dysfunction and immune dysregulation create a vicious cycle of chronic inflammation and neuronal damage, accelerating age-related cognitive decline.[12] Therapeutic approaches aimed at reducing microglial senescence, including senolytic therapy, may reduce neuroinflammation and restore microglial homeostasis, offering a promising avenue for age-related AD therapy.

Endoplasmic reticulum (ER) stress and apoptosis

The ER is crucial for protein folding, calcium homeostasis, and lipid synthesis. Under normal conditions, the ER maintains proteostasis via a tightly regulated quality control system. With aging, protein misfolding and metabolic stress increase, neurofibrillary tangles destabilize microtubules, and induce p-tau. Aβ is also produced through the overexpression of beta-site amyloid precursor protein-cleaving enzyme 1.[13]

A distinct initial imbalance or shock of aberrant proteins triggers apoptosis by activating caspases via extrinsic and intrinsic (mitochondrial) pathways, which ultimately results in cell death.[14] Through noradrenergic signaling, calcium dysregulation, and oxidative stress, aging makes neurons more susceptible to ER stress.[15]

Apolipoprotein E (APOE) hypothesis

APOE plays a role in the regular breakdown of

lipoproteins and the transport of fat and fat-soluble substances to the lymphatic system. It is initially synthesized in the brain and liver. The three alleles of the APOE gene (ε2=8%, ε3=77%, and ε4=15%) are found on chromosome 19. AD was also linked to APOE ε4.[16] APOE ε4 exacerbates glymphatic dysfunction by impairing AQP4 polarization[8], while also promoting neuroinflammation through microglial NF-κB activation.[16] This dual effect accelerates Aβ/tau accumulation, suggesting lipid-targeted therapies (e.g., bexarotene) may benefit ε4 carriers specifically. It also causes BBB disruption, synaptic and metabolic dysfunction.[6]

Aging alters the expression and function of ApoE, leading to reduced lipid transport efficiency, impaired neuronal repair, and increased vulnerability to neuroinflammation and Aβ accumulation, particularly in individuals carrying the ApoE ε4 allele.[17]

Neurotrophic factor hypothesis

Brain-derived neurotrophic factor (BDNF) is essential for immune system lifespan, learning, memory, and sleep.[18] The action of BDNF on tropomyosin receptor kinase B sustains long-term potentiation. Neuronal degeneration and impaired memory formation can result from changes in tropomyosin receptor kinase B receptor levels or BDNF expression.[19]

Both AD and aging are associated with a decline in BDNF expression and signaling, which exacerbates neurodegeneration by diminishing neuronal survival, growth, and repair mechanisms.[18] Therapeutic strategies to restore BDNF activity include physical exercise, cognitive training, and dietary polyphenols, which offer the potential to counteract synaptic loss and cognitive decline in aging and AD.

Excitotoxic hypothesis

Glutamate, an excitatory neurotransmitter, is essential for memory and learning. It has both ionotropic (NMDA) and metabotropic receptors. AD is influenced by the NMDA ionotropic glutamate receptors. During the resting membrane potential, magnesium ions block the voltage-dependent calcium channels of NMDA receptors. During depolarization, this barrier is removed, allowing calcium to enter the cell. The decrease in glutamate recycling in AD causes hyperexcitation of these receptors. These processes cause cell death and damage to neurons by increasing calcium influx.[20]

Glutamate transporter dysfunction, elevated synaptic glutamate levels, and excitotoxic susceptibility are all associated with aging.[21] Calcium-induced cell death cascades are accelerated in aging neurons due to a decreased mitochondrial buffer capacity.[20]

THERAPEUTIC IMPLICATIONS: TARGETING AGING TO TREAT ALZHEIMER'S DISEASE

Traditional therapeutic approaches for AD have primarily focused on reducing the Aβ burden or preventing p-tau aggregation. Despite decades of effort, these strategies have yielded limited clinical success rates. In contrast, targeting upstream aging mechanisms offers a new therapeutic paradigm involving interventions that delay, prevent, or even reverse AD-related processes. These interventions may include a variety of lifestyle adjustments, biological and medical therapies.

Lifestyle modifications

In order to maintain a normal weight and level of activity, lifestyle changes that incorporate physical activity, a balanced diet, restful sleep, stress management, and mental activity are generally safe and have been demonstrated to have neuroprotective effects. Table 1.

Physical activity

The most efficient non-pharmacological strategy to affect brain aging and AD risk is physical exercise, which includes morning gymnastics, walking, swimming, gardening, climbing stairs, and housework. Through the following processes, combined exercise training—including aerobic, strength, balance, and coordination training—as well as cognitive and social activities, appears to offer significant benefits to those with AD.[22]

First, by upregulating BDNF, insulin-like growth factor 1 (IGF-1), and vascular endothelial growth factor (VEGF), exercise antagonists alter AD by improving neuroplasticity and expanding hippocampus volume.[23] These elements play a role in normal hippocampal regeneration and angiogenesis (regulated by IGF-1 and VEGF) as well as learning (regulated by IGF-1 and BDNF).[22] It also enhances glymphatic clearance, promoting Aβ removal via AQP4-dependent mechanisms, which is particularly critical in APOE ε4 carriers.[24] BDNF depletion reduces TrkB-mediated synaptic resilience, worsening glutamate excitotoxicity. Exercise-induced BDNF upregulation may

Table 1: Anti-aging lifestyle interventions as therapeutic strategies for Alzheimer's disease

Category	Mechanism	Effect on AD/Aging	Ref.
Physical exercise	Increases BDNF, IGF-1, VEGF; increases glymphatic clearance (AQP4-dependent); reduces inflammation (NF-κB inhibition)	Enhances neurogenesis, reduces Aβ/tau, and improves cognition	[22-27]
Mediterranean/ MIND diet	Rich in omega-3s, polyphenols; reduces oxidative stress; modulates gut microbiota	Reduces Aβ aggregation, neuroinflammation, and cognitive decline	[30-32]
Caloric restriction (CR)	Activates SIRT1, AMPK; induces autophagy	Delays aging, reduces Aβ plaques, and improves mitochondrial function	[33-36]
Sleep optimization	Supports glymphatic Aβ/tau clearance during slow-wave sleep	Prevents protein accumulation, reduces neuroinflammation	[48-52]
Stress management	Normalizes HPA axis; reduces cortisol; increases BDNF	Reduces hippocampal atrophy, Aβ production, and neuroinflammation	[53,52]
Cognitive engagement	Increases synaptic plasticity, hippocampal neurogenesis, and increases BDNF	Strengthens cognitive reserve, slows Aβ/tau pathology	[55,54]

counteract this by enhancing calcium buffering.[22]

Secondly, it improves mitochondrial biogenesis and glucose metabolism, which counteracts cerebral hypometabolism.[25] Finally, it exerts anti-inflammatory, anti-immunity, antioxidant, hippocampal insulin signaling, autophagy, and gut microbial ecosystem.[26] Gamma-aminobutyric acid, Aktare, irisin, dopamine, and other chemicals are involved in these mechanisms.[27]

Exercise mimetics aim to replicate the cellular benefits of physical activity, such as mitochondrial biogenesis and insulin sensitivity, without physical exertion. However, they lack the full systemic effects of real exercise and may raise safety concerns with chronic use.

By promoting mitochondrial biogenesis and improving glucose metabolism, 5' adenosine monophosphate-activated protein kinase (AMPK) activator lowers Aβ accumulation and enhances brain energy balance.[28] Peroxisome proliferator-activated receptor delta agonists (e.g., GW501516) regulate lipid and glucose homeostasis in the brain, improving insulin sensitivity, restoring synaptic function, and reducing pro-inflammatory cytokines.[29]

However, despite the numerous mechanisms, further research is necessary to elucidate the exercise variables (including kind, volume, duration, and intensity) that influence AD.

Nutrition

In addition to providing vital nutrients for neuroprotection, eating a well-balanced diet full of fruits, vegetables, whole grains, lean meats, and healthy fats can help fight against insulin resistance, gut-brain axis dysfunction, and oxidative stress neuroinflammation.[5]

Delays in cognitive decline and a lower risk of AD are linked to nutritional strategies such as the Mediterranean diet, the Dietary Approaches to Stop Hypertension (DASH) diet, the Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND), and the Stop Hypertension (GUSTO) diet. These diets are high in fiber, plant-based polyphenols, omega-3 fatty acids, vitamins E and B12, and low in saturated fats and refined sugars, all of which modulate the hallmarks of aging and neurodegeneration.[30] Omega-3 (polyunsaturated fatty acid) is integral to neuronal membrane integrity and has been shown to reduce Aβ aggregation, suppress pro-inflammatory cytokine production, promote synaptic plasticity, and reduce the risk of cognitive decline.[28] Royal jelly provides neuroprotection against tau and Aβ aggregation, especially with ageing through synaptic signal transduction, antioxidant system enhancement, inflammation suppression, and increased neurotrophin production—all of which support normal neuronal structure and function.[31]

Dysbiosis with aging is linked to increased

permeability of the gut and BBB, promoting systemic inflammation and AD pathology—a process that can be attenuated by probiotic, prebiotic, or fecal microbiota transplantation.[32]

Reducing caloric intake by 20–60% without causing starvation is known as calorie restriction (CR). Mice's lifespan can be increased by up to 40% or more by delaying age-related diseases.[33] The degree of calorie restriction, the length of the diet, the age, sex, and general health status of the individual all affect how CR works.[34]

Mechanisms that directly prevent aging-related AD pathogenesis include SIRT1 gene activation, enhanced insulin sensitivity, and autophagy induction.[35] CR combined with intermittent fasting is more effective in improving cognitive function and reducing Aβ accumulation.[36] CR mimetics are substances that, without actually lowering caloric intake, attempt to replicate the physiological effects of calorie restriction. Natural substances, including resveratrol, curcumin, and quercetin, as well as pharmaceutical medications like metformin, glucagon-like peptide-1 receptor agonists, rapamycin, and spermidine, are examples of CR mimetics.[37]

Resveratrol, a natural polyphenolic chemical present in vegetables and fruits[28], has been shown to combat inflammation, oxidative stress, apoptosis, synaptic dysfunction, mitochondrial dysfunction, and angiogenesis.[37] Resveratrol also reduces Aβ aggregation, inhibits p-tau levels, and enhances mitochondrial biogenesis.[28] It has both physical activity and CR mimetics.

Metformin, a widely used AMPK activator for type 2 diabetes, promotes autophagy, reduces oxidative stress, and improves insulin sensitivity in the brain, counteracting insulin resistance often observed in early AD.[38] Some studies suggest that metformin reduces p-tau and neuroinflammation in animal models of AD.[34]

Rapamycin, a mammalian target of rapamycin (mTOR) inhibitor, delays brain aging by enhancing autophagy and lysosomal clearance of damaged proteins, including Aβ and p-tau. It also reduces microglial activation and inflammaging, which are exacerbated by age and contribute to cognitive decline.[37]

Spermidine, a polyamine with CR-mimetic properties, increases autophagy and exerts neuroprotective effects in AD models by decreasing tau fibrillation and Aβ burden, boosting mitochondrial function, and improving memory.[39]

Curcumin, the principal polyphenol in turmeric, exhibits anti-Aβ activity, antioxidant properties, anti-inflammatory effects, antiapoptotic functions, and modulation of cellular pathways through epigenetic processes. It binds to Aβ plaques, inhibits aggregation, promotes clearance, and modulates microglial activity.[40]

Combinatorial methods can be used to increase curcumin's therapeutic effectiveness. For example, curcumin and ascorbic acid together increase the anti-inflammatory response.[41]

Quercetin, a natural flavonoid found in fruits and vegetables, has antioxidant and anti-inflammatory effects.[42]

It produces its anti-inflammatory effects via activation of AMPK, which inhibits the activation of pro-inflammatory pathways. It also limits the damaging effects of inflammation on neuronal cells and improves mitochondrial function in mice with AD.[43] Quercetin also lowers Aβ aggregation, p-tau phosphorylation, and microglial activation. It restores acetylcholine levels through the inhibition of the hydrolysis of acetylcholine by the acetylcholinesterase enzyme.[44]

Genistein, a soy-derived isoflavone, mimics the estrogenic effects of estrogen, providing neuroprotection in postmenopausal women. It has multimodal properties, including antioxidant, anti-inflammatory, anti-amyloidogenic, anti-gut dysbiosis, pro-autophagy actions, and augmentation of neural plasticity.[45]

Anthocyanins in blueberries, blackberries, and purple corn are neuroprotective, antioxidant (reducing oxidative stress, inhibiting Aβ aggregation), anti-inflammatory (decreasing proinflammatory signals), antiapoptotic, protecting the BBB, and promoting cholinergic neurotransmission. They enhance synaptic signaling, improve spatial working memory, and reduce tau pathology.[46] The metabolic rate of anthocyanins varies among individuals, potentially affecting their overall effectiveness.[47]

Sleep

Sleep disruption affects the glymphatic system during slow-wave sleep, reducing the clearance of Aβ and p-tau.[48] It also increases pro-inflammatory cytokine levels, triggers ER stress, and disrupts synaptic homeostasis by reducing BDNF expression, leading to neurodegeneration and pathological progression.[49] Aging and AD disproportionately reduce slow-wave sleep, impair glymphatic system clearance, and create a vicious cycle of neurodegeneration.[50]

Recent human studies further highlight that poor sleep health accelerates brain aging. In a large cohort analysis, Miao *et al*.[51], demonstrated

that poor sleep quality was linked to older brain age, mediated by systemic inflammation and reduced neuroplasticity. This finding emphasizes that optimizing sleep may slow biological brain aging and potentially delay AD onset. Earlier work Lv *et al*.[52] also linked chronic insomnia and sleep fragmentation to greater amyloid deposition and tau phosphorylation in humans. Together, these results underscore the clinical importance of sleep restoration as a geroprotective intervention.

Stress management

Chronic psychological stress contributes to AD pathogenesis via neuroendocrine, inflammatory, and structural mechanisms. By disrupting the hypothalamic–pituitary–adrenal (HPA) axis, aging intensifies these effects by raising cortisol levels, which impair long-term potentiation, diminish neurogenesis, and cause hippocampal atrophy—all of which are critical for memory.[53] Additionally, glucocorticoids stimulate Aβ production, enhance p-tau, and impair Aβ clearance while activating NF-κB-mediated neuroinflammation and microglial dysfunction, contributing to inflammaging and neuronal death.[54]

It has been demonstrated that stress management techniques, including yoga, mindfulness, and cognitive behavioral therapy, raise BDNF expression, increase hippocampus volume, and return cortisol levels to normal.[53]

Mental activity

Maintaining intellectual activity and mental activities can be achieved by regularly participating in mental activities like crossword puzzles, education, reading books and magazines, puzzle organization, playing games like chess, board, checkers, and cards, and taking music courses. These types aid in enhancing visual memory, learning capacity, logical reasoning, attention, focus, and perceptiveness.[27]

Mechanistically, cognitive engagement enhances synaptic density, promotes dendritic complexity, upregulates BDNF, and supports hippocampal neurogenesis, creating structural resilience against neurodegeneration.[55] Cognitive enrichment has been demonstrated to lower Aβ burden and decrease functional decline in both human and animal models, including APOE ε4 carriers.[26]

Sociostation

Aging often leads to social isolation, comparatively more isolation, and loneliness. These psychosocial deficits exacerbate HPA axis dysregulation, elevate cortisol levels, induce hippocampal atrophy, and intensify neuroinflammation, all of which contribute to accelerated neurodegeneration and Aβ/p-tau pathology.[56]

Conversely, structured social programs—such as group therapy and intergenerational initiatives—improve mood and memory, reduce Aβ deposition, elevate BDNF expression, preserve long-term potentiation, and delay functional decline in AD patients.[57]

Creativity

Mechanistically, creative interventions such as music, art, and dance enhance emotional regulation, support cognitive performance, and boost levels of BDNF and nerve growth factor in AD patients. These effects are mediated by reduced neuroinflammation and stress pathways.[58]

In conclusion, the antiaging effects of AD may be enhanced by combining these lifestyle choices; however, even if lifestyle modifications appear promising, more research is required to confirm their safety, efficacy, recommended dosages, and potential interactions with other drugs.

Medical therapies *(Table 2)*

Acupuncture

Because acupuncture improves neuroinflammation, synaptic plasticity, nerve cell death, and the brain's synthesis and aggregation of Aβ, it can help with memory and cognitive impairment in AD. It is considered non-invasive, generally safe, and associated with improved cognitive markers in small-scale trials.[59]

Cellular senescence

It is defined as the irreversible growth arrest of damaged or stressed cells, which contributes significantly to age-related neurodegeneration through the release of the senescence-associated secretory phenotype (SASP)—a mixture of chemokines, proteolytic enzymes, and cytokines.[60]

Agents such as dasatinib, quercetin, and fisetin act as senolytics by targeting and removing aged or damaged cells associated with chronic inflammation. In mouse models of AD, these agents have been shown to reduce Aβ plaques, decrease tau aggregation, and improve cognitive performance.[61]

On the other hand, senomorphics like

rapamycin and metformin suppress the harmful SASP without inducing cell death, and have shown efficacy in reducing tau pathology and modulating neuroinflammation in preclinical settings.[37] There is some debate on the usefulness of senescence, despite its potential for treatment. Their inability to specifically eradicate senescent cells is the first drawback. Second, while senolytics may be less effective if used later, administering them too soon causes stem cell depletion, which speeds up the aging process and causes thrombocytopenia in the elderly. The type and quantity of senescent cells that should be eliminated for best results are also controversial.[61]

Epigenetic aging and reprogramming.

Age-related epigenetic changes, such as DNA methylation drift and histone modification alterations, can silence key neuroplasticity-related genes and are predictive of AD risk. Epigenetic clocks, especially the Horvath clock, serve as biomarkers of biological aging and correlate more closely with AD pathology than chronological age.[62]

Histone deacetylase inhibitors, such as sodium butyrate, have been shown to restore histone acetylation, increase BDNF expression, and improve memory performance in AD models.[63] More recently, partial epigenetic reprogramming using Yamanaka factors has demonstrated reversal of age-associated DNA methylation patterns, reduced Aβ pathology, and enhanced cognitive function in murine models without inducing tumorigenesis.[64]

Enhancing autophagy and proteostasis

Autophagy declines with age, leading to toxic protein accumulation. mTOR inhibition by rapamycin restores autophagy and reduces Aβ/p-tau pathology, improving cognition.[45] Natural compounds like spermidine, curcumin, and resveratrol also induce autophagy and show cognitive benefits.[28] Without adversely affecting other proteins such as the Notch receptor or amyloid precursor-like protein 1, the autophagy activator small-molecule enhancer of rapamycin-28 promotes the degradation of Aβ and the C-terminal segment of the amyloid precursor protein.[45]

Hormonal therapy

Neuroprotective substances include insulin-like growth factor-2, growth hormone-releasing hormone, gonadotropin-releasing hormone, and estrogen. Gonadotropin-releasing hormone slows down aging and encourages neurogenesis in mice.[3] In AD models, insulin-like growth factor-2 improves cognition by promoting neurogenesis and synaptogenesis.[65] To reduce neuroinflammation and other AD pathologies, estrogen shields neurons from Aβ toxicity and glutamatergic excitotoxicity. Additionally, it regulates transcription factors, including nuclear factor erythroid 2-related factor 2 and NF-κB, that are connected to inflammation and oxidative stress.[66]

Biological therapies.

In addition to repairing nerve damage in AD, neural stem cells (NSCs) can also slow down aging and neurodegenerative disorders because of their capacity to develop into neurons, astrocytes, and oligodendrocytes. They have been demonstrated to improve pathogenic events and behaviors in AD mice and to reduce neuroinflammation, synaptic, and metabolic dysfunctions.[67] Furthermore, enkephalinase (neprilysin), which is secreted by adipose-derived stem cells, can directly break down Aβ plaques.[68]

Young bone marrow transplantation helps older mice maintain synaptic connections, cytokine levels, and cognitive symptoms, extending their maximum lifespan by 30%.[69] However, the practical use of bone marrow transplantation is restricted by transplant rejection and the scarcity of young bone marrow donors.[68]

In addition to reducing soluble Aβ levels in the blood and Aβ plaques in the brains of aged rats, whole blood replacement dramatically improves spatial memory.[70] Delivering a wider variety of antiaging agents that target several aging markers simultaneously is made possible by blood rejuvenation. Although it necessitates an adequate blood supply and may result in negative reactions, this strategy might be more effective.[4]

Clinically, the AMBAR (Alzheimer's Management by Albumin Replacement) trial explored plasma exchange with albumin and intravenous immunoglobulin in AD patients. The results, demonstrated stabilization of cognitive decline in mild-to-moderate AD, suggesting modulation of peripheral Aβ and inflammatory mediators may confer benefit. These data provide an important translational bridge between animal blood-replacement models and feasible human plasma-based interventions. Further investigation of optimized dosing, donor age, and combination

Table 2: Anti-aging pharmacological and biological therapies as the therapeutic strategies for Alzheimer's disease

Category	Intervention	Mechanism	Stage of Evidence
Senolytics	Dasatinib + quercetin Fisetin	Clears senescent microglia	Dasatinib + quercetin (phase 2) Fisetin (Phase 1) [61]
CR mimetics	Resveratrol	Activates SIRT1, autophagy	(Phase 3) human trials [28]
Epigenetic modulators	Sodium butyrate	↑ Histone acetylation, BDNF	Preclinical, improves memory [63]
Epigenetic reprogramming	Yamanaka factors	Resets DNA methylation	Preclinical (mice) [64]
Stem cells	Neural stem cells	Secretes neurotrophic factors	Mouse models show Aβ reduction [67]
Young plasma	Plasma exchange	Rejuvenates systemic factors	Pilot trials show safety [71]
Gut microbiota	Fecal transplant	Reduces neuroinflammation	Reversed aging in mice [72]

with senolytic or anti-inflammatory agents is warranted.[71]

When the gut microbiota of young mice is transplanted into older animals, immunosenescence and neuroinflammation are reversed, and hippocampal neurogenesis, behavior, and cognition are all improved.[72] (Table 2)

Despite encouraging preclinical data, challenges remain. Ethical concerns, risk of tumorigenesis, immune rejection, and low survival rates post-transplantation must be addressed before clinical translation.

Other possible therapies

Nonsteroidal anti-inflammatory drugs like Ibuprofen, antiviral medications like valacyclovir and some antibiotics, mitochondrial function regulators like nilotinib, metabolic activators like L-serine, N-acetyl cysteine, nicotinamide riboside, and L-carnitine tartrate, neural repair medications like CT1812 and simufilam, and antioxidants have been shown to have a neuroprotective effect and are being investigated for the treatment of AD.[4,73]

FUTURE DIRECTIONS AND CONCLUSION

Alzheimer's disease can be viewed not just as a neurodegenerative condition but as a manifestation of accelerated brain aging. By targeting the root causes of aging through a geroscience framework, we have the opportunity to delay or even prevent AD onset. Rather than targeting downstream symptoms alone, emerging strategies seek to intervene earlier in the disease course by addressing the biological aging mechanisms that drive AD pathogenesis.

Future research should focus on integrated, multimodal interventions that combine lifestyle modification with pharmacological and biological therapies. Tailored approaches—based on genetic risk profiles (e.g., APOE status), comorbidities, and individual aging trajectories—may optimize clinical outcomes. To evaluate the long-term safety and effectiveness of innovative treatments like senolytics, epigenetic modulators, and stem cell-based therapies in older populations, extensive, longitudinal clinical trials are also required. Developments in biological age biomarkers, machine learning, and systems biology have the potential to improve risk assessment and therapy customization.

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