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Advances in Herbal Nootropics for Dementia: Targeting Oxidative Stress, Neuroinflammation, and Cognitive Decline

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Abstract:

Herbal nootropics are gaining attention for their multi-target strategy in dementia, which offers neuroprotection along with antioxidant and anti-inflammatory actions. The current therapies only provide symptomatic relief without halting or altering disease progression, which occurs due to a complex interplay of amyloid and tau pathology, oxidative stress, deficiency of neurotransmitters, neuroinflammation and vascular damage. The worldwide growing burden of dementia highlights the need for safer, affordable and mechanistically broader therapies.

Herbal nootropics like *Bacopa monnieri, Gingko biloba, Curcuma longa* and many more acts on variety of targets such as acetylcholinesterase inhibition, modulation of signalling but primarily they enhance cognition by modulating neurotransmission, improve brain energy metabolism, support neuroplasticity and reduce oxidative and inflammatory stress.

Preclinical research demonstrates improvements in learning and memory from herbal nootropics. However, the lack of standardization and large-scale trials restrict their clinical translation. Future work should focus on standardized extracts, interaction assessments and rational integration with conventional treatment for evidence-based roles of herbal nootropics in dementia.

Keywords: Herbal nootropics; vitamin B12; vascular damage; neuroplasticity; *Bacopa monnieri*

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1. Introduction to Dementia

Everyone knows dementia, but few truly understand its complexity. Dementia is a syndrome characterized by a decline in cognitive function severe enough to interfere with daily activities and independent living. According to the World Health Organization (WHO), dementia results from various diseases and injuries that affect the brain, leading to a chronic or progressive deterioration in cognitive abilities. Patients experience impairments in memory, thinking, learning, language, calculation, judgment, and comprehension. Although dementia predominantly affects older adults, particularly those over 65 years of age, it is not a normal consequence of aging. Multiple factors contribute to its development, including genetic predisposition, cerebrovascular disease, infections, traumatic brain injury, metabolic disorders, and nutritional deficiencies such as vitamin B12 deficiency.

Dementia is characterized by a progressive, global, and often irreversible decline in cognitive abilities, including memory, reasoning, language, and behavior. It extends beyond simple forgetfulness and affects multiple domains of brain function. Patients may experience memory loss, impaired thinking, language difficulties, poor judgment, and reduced ability to perform everyday tasks. Diagnosis is typically established through a combination of clinical history, cognitive assessment, laboratory investigations, and neuroimaging techniques such as magnetic resonance imaging (MRI). Although some causes of cognitive impairment may be reversible when identified and treated early, most forms of dementia are progressive and disabling. As the disease advances, affected individuals become increasingly dependent on caregivers for daily activities and personal care.

Dementia should not be confused with delirium. Delirium develops rapidly, fluctuates throughout the day, and is often reversible with treatment of the underlying cause. In contrast, dementia develops gradually and progressively worsens over time. Dementia may coexist with other conditions such as depression, Parkinsonism, or other neurological disorders. Ultimately, dementia affects not only memory but also multiple aspects of cognition, behavior, personality, and functional independence[1].

2. Classification of Dementia

Dementia encompasses a heterogeneous group of disorders and can be classified according to anatomical involvement, etiopathogenesis, and clinical-neuropsychological characteristics.

2.1 Anatomical Classification

Cortical Dementia

Cortical dementia primarily affects the cerebral cortex, the outer layer of the brain responsible for higher cognitive functions. Clinical manifestations include impaired memory encoding, aphasia

(language impairment), agnosia (inability to recognize familiar objects), apraxia (difficulty performing learned motor tasks), and deficits in abstract thinking. Memory impairment is generally attributed to a storage deficit. Common examples include Alzheimer's disease, frontotemporal dementia, and Creutzfeldt–Jakob disease.

Subcortical Dementia

Subcortical dementia affects structures beneath the cerebral cortex, including the basal ganglia, thalamus, white matter, and brainstem. Clinical features include impaired concentration, slowed thinking (bradyphrenia), movement disorders, executive dysfunction, and mood disturbances. Memory deficits are primarily related to impaired retrieval rather than storage. Associated disorders include Parkinson's disease, Huntington's disease, vascular dementia, and progressive supranuclear palsy.

2.2 Classification Based on Etiopathogenesis

Reversible Dementia

Reversible dementia results from conditions that can be corrected or significantly improved through appropriate treatment. These conditions are often acute or subacute and may arise from metabolic disturbances, infections, toxic exposures, endocrine disorders, or nutritional deficiencies. Cognitive impairment typically includes inattention, slowed information processing, and mild-to-moderate memory deficits, which may improve after treatment of the underlying cause. Examples include hypothyroidism-associated cognitive impairment and drug-induced dementia.

Irreversible Dementia

Irreversible dementia is characterized by progressive and permanent cognitive decline that cannot be fully reversed. It usually develops gradually and worsens over time. Cognitive deficits include severe memory impairment, aphasia, visuospatial dysfunction, and executive impairment. Common examples include Alzheimer's disease and Huntington's disease.

2.3 Clinical and Neuropsychological Spectrum

Alzheimer's Disease

Alzheimer's disease (AD) is the most common cause of dementia and typically develops insidiously. It is characterized by the accumulation of β-amyloid plaques and neurofibrillary tangles, accompanied by a reduction in acetylcholine due to degeneration of basal forebrain cholinergic neurons. Clinical manifestations include episodic memory loss, visuospatial impairment, temporal disorientation, language deficits, and progressive loss of functional independence.

Vascular Dementia

Vascular dementia results from impaired cerebral blood flow leading to brain tissue injury and neuronal loss. Reduced blood supply may occur due to stroke, vascular occlusion, or cerebral hemorrhage. Clinical features include executive dysfunction, slowed cognitive processing, impaired concentration, mood disturbances, gait abnormalities, balance problems, and urinary symptoms. Memory impairment is often less pronounced than in Alzheimer's disease.

Mixed Dementia

Mixed dementia refers to the coexistence of two or more dementia pathologies in the same individual. The most common combination is Alzheimer's disease with vascular dementia. Multiple pathological processes occurring simultaneously may accelerate cognitive decline beyond that caused by a single disease process.

Frontotemporal Dementia

Frontotemporal dementia (FTD) is a neurodegenerative disorder characterized by early changes in personality, behavior, executive function, and language. It is associated with abnormal accumulation of proteins such as tau, TDP-43, and FUS. Clinical manifestations include impaired judgment, loss of social awareness, emotional blunting, behavioral disinhibition, executive dysfunction, and progressive language impairment.

Dementia with Lewy Bodies

Dementia with Lewy bodies (DLB) is the second most common neurodegenerative dementia and results from abnormal accumulation of α-synuclein-containing Lewy bodies in the cortex and brainstem. It affects cognition, behavior, alertness, and motor function. Clinical features include fluctuating cognition, recurrent visual hallucinations, bradykinesia, REM sleep behavior disorder, and Parkinsonian motor symptoms[2,3].

3. Historical Perspective

Historical descriptions of dementia-like disorders can be traced back to the writings of Avicenna (Ibn Sina), who categorized cognitive impairments into disturbances of memory, thinking, and imagination. He described three principal forms: Fisad-al-Zekr (memory impairment), Fisad-al-Fekr (impaired judgment), and Fisad-al-Takhayol (disturbance of imagination). These descriptions bear remarkable similarities to modern classifications of Alzheimer's disease, frontotemporal dementia, and Lewy body dementia. Avicenna also recognized potential causes of cognitive impairment, including head trauma, fever, nutritional deficiencies, and systemic organ dysfunction centuries before the advent of modern neuroimaging technologies[4].

3.1 Consensus and Emerging Classification

Contemporary classification systems, including the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) and the Vascular Impairment of Cognition Classification Consensus Study (VICCCS), have adopted a spectrum-based approach that includes concepts such as mild and major vascular cognitive impairment, with post-stroke dementia recognized as an important subtype. Modern diagnostic frameworks increasingly emphasize disease continua rather than rigid categorical classifications[5].

3.2 Global Epidemiology of Dementia

Dementia has emerged as one of the leading causes of disability, dependency, and mortality worldwide. Its prevalence is increasing rapidly due to population aging and longer life expectancy. Currently, approximately 57 million individuals worldwide are living with dementia, and this number is projected to reach approximately 153 million by 2050. Nearly 10 million new cases are diagnosed annually. Countries with rapidly aging populations, including Japan, Italy, Germany, and China, experience particularly high prevalence rates. However, the burden is increasingly shifting toward low- and middle-income countries, especially in Asia and Africa.

Advancing age remains the strongest risk factor for dementia, and women are disproportionately affected compared with men. This difference is largely attributed to longer female life expectancy. In countries such as Japan, where nearly one-third of the population is older than 65 years, dementia has become a major public health challenge requiring extensive healthcare and social support systems.

Several modifiable risk factors contribute to dementia development, including diabetes mellitus, hypertension, obesity, smoking, physical inactivity, social isolation, and lower educational attainment. Although age-standardized dementia rates have remained relatively stable in some regions, the absolute number of affected individuals continues to increase because of global population aging. The fastest growth is anticipated in low-resource regions where underdiagnosis and limited healthcare access remain substantial barriers. Consequently, dementia represents one of the most significant healthcare challenges of the twenty-first century[6–8].

4. Socioeconomic Burden of Dementia

Dementia imposes a substantial burden not only on affected individuals but also on families, healthcare systems, and national economies. The financial impact has been described as an iceberg, where visible healthcare expenditures represent only a fraction of the total burden. Using the value-of-statistical-life (VSL) approach, the global economic cost of dementia was estimated at approximately US$2.8 trillion in 2019 and is projected to rise to nearly US$17 trillion by 2050[9,10].

Direct costs, including hospitalizations, long-term care, nursing home services, and medications, have increased steadily over recent decades. However, indirect costs such as productivity losses, psychological distress, reduced quality of life, and the unpaid contributions of family caregivers often remain underrecognized. Many families experience significant financial strain while simultaneously coping with the emotional challenges associated with caring for a loved one with dementia. Family members provide the majority of dementia care worldwide, frequently at the expense of their own physical, emotional, and economic well-being[9,10].

Dementia is among the most costly and burdensome health conditions globally, yet funding for dementia research and support services remains disproportionately low compared with its societal impact. Governments and healthcare systems continue to face challenges in addressing the growing prevalence of dementia amid limited resources and increasing demand for long-term care services[9,10].

The burden of dementia varies across regions. In high-income countries, dementia places considerable pressure on healthcare budgets and long-term care infrastructures. In many low- and middle-income countries, however, limited diagnostic capabilities and inadequate healthcare resources result in most caregiving responsibilities being assumed by family members. Countries such as China, India, and Brazil are expected to contribute substantially to future global dementia-related costs due to their large and aging populations. By 2050, more than two-thirds of individuals living with dementia are expected to reside in community settings, further emphasizing the need for accessible support systems and healthcare services. Consequently, dementia represents not only a major medical challenge but also a critical economic and social concern requiring coordinated global action[9,10].

4.1 Limitations of Current Treatment

Current pharmacological therapies for dementia primarily provide symptomatic relief rather than disease modification. Commonly prescribed medications, including donepezil, galantamine, rivastigmine, and memantine, may temporarily improve cognitive function or slow symptom progression, but they do not halt or reverse the underlying neurodegenerative process[11].

One of the major obstacles in dementia treatment is the blood-brain barrier (BBB), which restricts the delivery of many therapeutic agents to the central nervous system. Furthermore, neuronal damage and loss that occur during disease progression are largely irreversible. Although higher drug doses may improve therapeutic exposure, they are often associated with adverse effects such as nausea, vomiting, headache, dizziness, and fatigue[11].

Many patients are diagnosed only after significant neuronal loss has occurred, reducing the effectiveness of available therapies. In addition, numerous investigational drugs that demonstrated promise in preclinical studies have failed during clinical trials. While some therapies can reduce pathological hallmarks such as amyloid plaques, these effects have not consistently translated into

meaningful clinical improvements. Even recently developed immunotherapeutic approaches have generally produced modest benefits, highlighting the need for more effective treatment strategies[11]. Non-pharmacological interventions, including regular physical activity, healthy dietary habits, cognitive stimulation, and social engagement, may contribute to maintaining cognitive health and delaying disease progression. However, these approaches require long-term adherence and their effectiveness varies among individuals[11].

4.2 The Need for Alternatives

Given the limitations of existing therapies, there is an urgent need for innovative treatment approaches capable of overcoming biological barriers and delivering therapeutics more effectively to affected brain regions. Advanced drug delivery systems such as nanoparticles, nanoliposomes, exosomes, and other nanocarriers have emerged as promising strategies for improving drug transport across the blood-brain barrier and enhancing therapeutic targeting of diseased neurons[12]. These technologies offer the potential to increase drug bioavailability, reduce systemic adverse effects, and improve treatment efficacy. Emerging approaches including gene therapy, gene editing technologies, and antibody-based therapeutics are also being investigated as potential disease-modifying interventions. Although these strategies remain expensive and technically challenging, they represent important avenues for future dementia treatment development[12].

Lifestyle-based interventions, dietary modifications, omega-3 fatty acid supplementation, cognitive training, and multidomain preventive programs may further contribute to reducing dementia risk and supporting cognitive function. Future management strategies will likely involve integrated approaches that combine pharmacological therapies, advanced delivery technologies, lifestyle interventions, and personalized medicine. Continued investment in research and innovation is essential to address the growing global burden of dementia and improve patient outcomes[12].

5. Introduction to Nootropics

Nootropics, commonly referred to as cognitive enhancers or “smart drugs,” comprise a diverse group of natural, synthetic, and nutritional substances that may improve cognitive performance, memory, attention, learning, and overall brain function. Interest in nootropics has increased substantially due to the growing prevalence of neurodegenerative disorders and the limited effectiveness of existing therapeutic options[13].

In neurodegenerative diseases such as dementia, progressive neuronal loss leads to declines in memory, cognition, and functional independence. Because currently available treatments provide only modest symptomatic benefits, considerable attention has shifted toward compounds that may protect neurons, enhance cognitive performance, and support brain health. Although nootropic agents are not considered cures for neurodegenerative diseases, they may contribute to symptom management and neuroprotection when used appropriately[13].

5.2 The Growing Relevance of Nootropics

Nootropics have gained popularity among both healthy individuals seeking cognitive enhancement and patients with neurological disorders. These compounds may be derived from medicinal plants, synthetic pharmaceuticals, dietary supplements, or functional foods. Their growing relevance stems from the increasing demand for safe and effective interventions that support memory, attention, learning, and overall cognitive performance[14, 15].

Neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, and other forms of dementia involve progressive neuronal dysfunction and loss. Various natural nootropics, including *Bacopa monnieri*, *Ginkgo biloba*, *Withania somnifera* (Ashwagandha), and *Panax ginseng*, have been extensively investigated for their neuroprotective properties. These compounds may exert antioxidant, anti-inflammatory, anti-apoptotic, and neurotransmitter-modulating effects that contribute to cognitive support[14, 15].

Synthetic nootropics, including piracetam and related racetam derivatives, have also been explored for their ability to influence neurotransmission and cognitive performance. Although evidence from clinical studies remains variable, ongoing research continues to evaluate their potential therapeutic value in neurodegenerative conditions. Traditional medical systems such as Ayurveda and Traditional Chinese Medicine have long incorporated cognitive-enhancing herbs, many of which are now being investigated using modern scientific approaches. Polyherbal formulations may be particularly advantageous due to their ability to simultaneously target multiple pathological pathways involved in cognitive decline[14, 15].

5.3 Mechanistic Perspective

The mechanisms underlying nootropic activity are multifaceted and often involve simultaneous modulation of several biological pathways. Many nootropics exert antioxidant effects that reduce oxidative stress and protect neurons from free radical-mediated damage. Others possess anti-inflammatory properties that help attenuate neuroinflammation, a key contributor to neurodegenerative disease progression[16, 17].

Nootropics may also improve mitochondrial function, enhance cerebral blood flow, and regulate neurotransmitter systems including acetylcholine, dopamine, glutamate, and serotonin. Some compounds have demonstrated the ability to reduce the accumulation or toxicity of pathological proteins such as amyloid-β, tau, and α-synuclein. Emerging evidence further suggests that certain nootropics may influence the gut-brain axis through modulation of gut microbiota composition and activity[16, 17].

Medicinal plants such as *Withania somnifera*, *Bacopa monnieri*, and *Curcuma longa* often exhibit multitarget actions, simultaneously affecting oxidative stress, inflammation, neurotransmission, and cellular survival pathways. Synthetic agents such as piracetam primarily influence neuronal membrane fluidity, neurotransmitter release, and ion channel function. Together, these

mechanisms may provide comprehensive support for cognitive function and neuronal resilience[16,17].

5.5 Historical Perspective on Nootropics

The concept of enhancing cognitive performance has existed for centuries across various cultures and traditional medical systems. Natural substances believed to improve memory, concentration, and mental clarity have long been incorporated into daily diets and medicinal practices. Historical examples include the use of rosemary in ancient Greece and numerous herbal remedies in Ayurvedic and Traditional Chinese Medicine for supporting brain health[18].

The modern scientific concept of nootropics emerged in 1972 when Romanian psychologist and chemist Corneliu E. Giurgea introduced the term "nootropic," derived from the Greek words *nous* (mind) and *tropein* (to bend or turn). Giurgea proposed that a true nootropic should enhance learning and memory, protect the brain against physical and chemical injury, improve neuronal efficiency, and exhibit minimal toxicity or adverse effects[18].

Since then, nootropics have evolved into a broad category encompassing natural products, synthetic compounds, vitamins, nutraceuticals, and functional foods. These agents are being investigated for applications in conditions such as dementia, Alzheimer's disease, attention-deficit/hyperactivity disorder (ADHD), and age-related cognitive decline. Although the precise mechanisms of many nootropics remain incompletely understood, growing scientific evidence continues to support their potential role in promoting cognitive health and neuroprotection[18].

5.6 Classification of Nootropics

There are so many varied categories of nootropics though effectively they can be broken into two main groups. synthetic and natural, they both offer great rewards.

These are lab-grown and lifeless, if pure, and highly controlled. These drugs provide precise dose, potent action, and occasionally also big risks. They are not natural, but science likes predictability and these are precise.

Compound	Example	Mechanisms
Racetams	Piracetam, aniracetam	Membrane fluidity, AMPA modulation, acetylcholine up
Ampakines	CX-516, Sunifiram	Increases glutamate, AMPA receptor modulation
Cholinergics	Donepezil, Huperzine A	Cholinesterase inhibition, acetylcholine up
Dopamine Modulators	Selegiline, Methylphenidate	Monoamine oxidase inhibition, DA/NE reuptake block

Others	Centrofenoxine, Mexidol	Antioxidant, vasodilator, mitochondrial support

These are all synthetic drugs and are commonly prescribed for conditions such as dementia, ADHD Parkinson even in the general population to increase focus and attention. They can have powerful effects, but also side effects: insomnia, nausea, addiction, anxiety. Whether "good" or "bad," they involve both benefits and real risks1[9].

Herbs, roots, leaves are the remnants of traditional medicine. They are not always as potent as synthetic drugs but are gentle with fewer risks and offers wide range of options, each with their own effects and long history of use. But the results sometimes feel a bit like chances as the active ingredient, dosage and purity can differ in different batches. Even so they are more popular and considered as more natural due to their low risks[20].

Plant/Compound	**Uses**	**Mechanisms**
Bacopa monnieri	Memory, stress	Cholinergic modulation, antioxidants
Ginkgo biloba	Dementia, circulation	Vasodilator, antioxidant, anti-amyloid
Panax ginseng	Energy, cognition	Neurotransmitter regulation, antioxidants
L-Theanine	Relaxation, focus	Dopamine, serotonin, GABA modulation
Ashwagandha	Stress, neuroprotection	GABA-mimetic, anti-inflammatory
Huperzine A	Alzheimer's, memory	Cholinesterase inhibition, anti-oxidant

6. Synthetic vs Herbal [(21)]

Feature	**Synthetic Nootropics**	**Herbal/Natural Nootropics**
Source	Laboratory, chemical synthesis	Plant, root, leaf, sometimes animal
Dose & Purity	Consistent, precise	Variable, may be contaminated
Mechanism	Single target, clear mechanism (mostly)	Multiple targets, complex polypharmacology
Risks	Sometimes high (side effects, addiction)	Usually mild, less toxic, but unpredictable

Availability	Prescribed or synthetic, controlled	Over the counter, supplements, food, easy

5.4 Mechanism of Cognitive Enhancement with Nootropics

Nootropics, commonly referred to as cognitive enhancers or "smart drugs," support brain function through multiple complementary mechanisms rather than a single biological pathway. These compounds may improve memory, attention, learning, executive function, and overall cognitive performance by modulating neurotransmitter systems, enhancing neuronal energy metabolism, protecting against neurodegeneration, promoting neuroplasticity, and improving cerebral blood flow. Their multifaceted mode of action makes them particularly attractive for managing age-related cognitive decline and neurodegenerative disorders such as Alzheimer's disease and dementia[22–25].

5.4.1 Neurotransmitter Modulation

One of the primary mechanisms of nootropic action involves the regulation of neurotransmitter systems that govern cognition and behavior. Many nootropics enhance cholinergic neurotransmission by increasing acetylcholine (ACh) availability through inhibition of acetylcholinesterase (AChE), thereby improving memory formation, learning capacity, and information processing. Synthetic agents such as methylphenidate increase dopamine and norepinephrine levels within the prefrontal cortex, leading to enhanced attention, working memory, motivation, and executive functioning. Other nootropics influence glutamatergic signaling through N-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, facilitating synaptic plasticity and long-term potentiation (LTP), which are essential processes underlying memory consolidation and learning[22–25].

5.4.2 Enhancement of Energy Metabolism

Several nootropic compounds improve neuronal energy production by supporting glucose utilization and mitochondrial function. Adequate energy supply is critical for maintaining synaptic transmission, neuronal communication, and cognitive performance. Piracetam and related racetam derivatives have been shown to improve neuronal membrane fluidity and enhance mitochondrial efficiency, particularly in aging brains. By optimizing cellular energy metabolism, these agents help maintain neuronal viability and support cognitive function under conditions of metabolic stress[22–25].

5.4.3 Neuroprotective Effects

Neuroprotection represents another important mechanism through which nootropics exert beneficial effects. Many natural and synthetic nootropics possess antioxidant and anti-inflammatory properties that reduce oxidative stress, neuroinflammation, and excitotoxic neuronal damage. These actions may slow age-related cognitive decline and protect against neurodegenerative processes. Certain compounds have also demonstrated the ability to reduce the accumulation of toxic protein aggregates, including amyloid-β peptides and tau proteins, which are strongly implicated in the pathogenesis of Alzheimer's disease. Preservation of synaptic integrity and neuronal survival contributes significantly to their cognitive benefits[22–25].

5.4.4 Promotion of Neuroplasticity and Synaptic Function

Nootropics may enhance brain plasticity by stimulating neurogenesis, increasing synaptic density, and modulating receptor activity. Several natural nootropics, including *Panax ginseng*, *Curcuma longa* (curcumin), and *Bacopa monnieri*, have been reported to increase the expression of neurotrophic factors such as brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF). These molecules play critical roles in neuronal growth, differentiation, synaptic remodeling, and long-term cognitive function. Enhanced neuroplasticity supports learning, memory retention, and recovery from neuronal injury[22–25].

5.4.5 Improvement of Cerebral Blood Flow

Certain nootropics improve cognitive performance through vascular mechanisms. Herbal compounds such as *Ginkgo biloba* possess vasodilatory properties that enhance cerebral circulation, increasing the delivery of oxygen and nutrients to metabolically active brain regions. Improved cerebral perfusion supports neuronal metabolism, cognitive processing, and overall brain health. Enhanced blood flow may be particularly beneficial in aging individuals and patients with cerebrovascular insufficiency, where reduced cerebral perfusion contributes to cognitive impairment[22–25].

Collectively, these mechanisms demonstrate that nootropics exert cognitive-enhancing effects through a complex interplay of neurotransmitter regulation, metabolic support, neuroprotection, neuroplasticity promotion, and vascular optimization. This multitargeted mode of action underlies their growing interest as potential therapeutic agents for cognitive decline, neurodegenerative diseases, and age-associated neurological disorders[22–25].

Examples of Mechanistic Actions by Compound

Mechanism	Example Compound(s)	Action Summary

Acetylcholinesterase Inhibition	Huperzine A, Donepezil	Boost brain acetylcholine to aid memory
Dopamine & Noradrenaline Modulation	Methylphenidate, Amphetamines	Increase catecholamines to improve focus and working memory
Glutamate Receptor Modulation	Aniracetam, Piracetam	Enhance NMDA/AMPA receptor function, promote LTP
Mitochondrial & Membrane Fluidity	Piracetam	Improve energy metabolism and neuronal signaling
Antioxidant & Anti-inflammatory	Bacopa monnieri, Ginkgo biloba	Protect neurons by reducing oxidative damage
Increase Neurotrophic Factors	L-Theanine, Ashwagandha	Promote BDNF and NGF, supporting synaptic plasticity
Vasodilation	Ginkgo biloba	Improve oxygen and nutrient brain supply

6. Pathophysiology of Dementia

Dementia is a clinical syndrome characterized by progressive cognitive decline resulting from multiple underlying pathological processes. Neurodegenerative disorders, particularly Alzheimer's disease (AD), account for the majority of dementia cases and are characterized by disturbances in protein metabolism, synaptic dysfunction, and neuronal loss. The pathological hallmarks of AD include the accumulation of amyloid-beta (Aβ) peptides and abnormal tau protein aggregates, which interact to drive neurodegeneration and cognitive impairment[26].

6.1 Neurodegenerative Mechanisms

6.1.1 Amyloid-Beta Pathology

Amyloid precursor protein (APP) is a transmembrane glycoprotein involved in neuronal growth, repair, and synaptic function. APP undergoes proteolytic processing through either a non-amyloidogenic pathway involving α- and γ-secretases or an amyloidogenic pathway involving β- and γ-secretases. The amyloidogenic pathway generates amyloid-beta peptides, primarily Aβ40 and the more aggregation-prone Aβ42 isoform. Excessive production or impaired clearance of Aβ42 results in the formation of soluble oligomers, fibrils, and extracellular senile plaques within the brain[27,28].

Aβ oligomers are considered the most neurotoxic species because they disrupt synaptic transmission, alter calcium homeostasis, impair mitochondrial function, induce oxidative stress, and trigger neuroinflammatory responses. These pathological events ultimately lead to synaptic

dysfunction, neuronal loss, and progressive cognitive decline. However, the relatively weak correlation between plaque burden and disease severity suggests that additional pathological mechanisms contribute to dementia progression[27,28].

6.1.2 Tau Protein Abnormalities

Tau is a microtubule-associated protein that stabilizes neuronal microtubules and maintains axonal transport. The MAPT gene produces multiple tau isoforms through alternative splicing, ensuring balanced expression in healthy adult brains. Under pathological conditions, tau undergoes abnormal post-translational modifications, particularly hyperphosphorylation mediated by kinases such as glycogen synthase kinase-3 (GSK-3) and cyclin-dependent kinase 5 (CDK5). Hyperphosphorylated tau dissociates from microtubules, leading to cytoskeletal instability and the formation of paired helical filaments that aggregate into neurofibrillary tangles (NFTs)[29].

The burden of NFTs correlates strongly with neuronal loss and cognitive impairment. Tau pathology progresses in a predictable pattern, spreading from the entorhinal cortex to the hippocampus and neocortex through trans-synaptic, prion-like mechanisms. This propagation disrupts neuronal transport systems, impairs mitochondrial function, promotes neuroinflammation, and contributes significantly to cognitive deterioration[29].

6.1.3 Interplay Between Amyloid-Beta and Tau

Emerging evidence suggests that amyloid-beta and tau pathology act synergistically to accelerate neurodegeneration. According to the amyloid cascade hypothesis, Aβ accumulation initiates a sequence of pathological events that promote tau hyperphosphorylation and aggregation. Experimental studies indicate that Aβ oligomers facilitate tau pathology, while abnormal tau further enhances Aβ toxicity and synaptic dysfunction. Together, these proteins disrupt neuronal signaling, gene expression, and synaptic integrity, resulting in progressive cognitive decline[20].

Furthermore, therapeutic studies have demonstrated that reducing Aβ burden may attenuate tau pathology and vice versa. These findings support the development of combination therapies targeting both pathological proteins simultaneously as a potentially effective strategy for slowing disease progression[30].

6.1.4 Additional Pathogenic Factors

In addition to amyloid-beta and tau pathology, several other mechanisms contribute to dementia development. Chronic neuroinflammation, characterized by microglial activation and cytokine release, promotes neuronal injury and synaptic loss. Genetic factors, particularly the apolipoprotein E4 (APOE4) allele, influence amyloid aggregation, tau pathology, and disease susceptibility. Mitochondrial dysfunction, impaired cellular metabolism, and oxidative stress further exacerbate neuronal degeneration and accelerate cognitive decline[30].

6.2 Oxidative Stress in Dementia

Oxidative stress results from an imbalance between reactive oxygen species (ROS) production and the body's antioxidant defense systems. Major ROS include superoxide anions, hydroxyl radicals, and hydrogen peroxide, which are generated primarily through mitochondrial respiration and enzymatic pathways such as NADPH oxidase activity. While low levels of ROS participate in physiological cellular signaling, excessive ROS accumulation damages lipids, proteins, nucleic acids, and cellular organelles[31].

The brain is particularly vulnerable to oxidative injury because of its high oxygen consumption, abundant polyunsaturated fatty acids, elevated metal ion concentrations, and relatively limited antioxidant defenses. Oxidative stress is recognized as an early and persistent feature of dementia and is closely associated with amyloid-beta accumulation and tau hyperphosphorylation. Elevated levels of oxidative damage markers, including malondialdehyde, 4-hydroxynonenal, protein carbonyls, and oxidized nucleic acids, have been detected in the brains, cerebrospinal fluid, and plasma of patients with dementia[31].

ROS contribute to mitochondrial dysfunction, synaptic impairment, and neuronal apoptosis. Oxidative stress also activates kinases such as GSK-3, promoting tau hyperphosphorylation and neurofibrillary tangle formation. Consequently, oxidative stress acts as a central driver of neurodegeneration and cognitive decline[31].

7. Neuroinflammation and Microglial Activation

Neuroinflammation represents a critical component of dementia pathogenesis and involves activation of resident glial cells, particularly microglia and astrocytes, in response to injury, protein aggregation, and disrupted brain homeostasis. Activated microglia release pro-inflammatory cytokines, including interleukin-1β (IL-1β), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), reactive oxygen species, and chemokines that contribute to an inflammatory microenvironment[32,33].

Initially, microglial activation serves a protective role by promoting the clearance of amyloid-beta and tau aggregates. However, prolonged activation becomes detrimental and contributes to synaptic dysfunction, neuronal loss, and disease progression. The NADPH oxidase enzyme complex, particularly NOX2, serves as a major source of microglial-derived ROS. Activation of pattern recognition receptors such as toll-like receptor 4 (TLR4) and complement receptor 3 stimulates NOX2-mediated superoxide production, amplifying inflammatory signaling pathways including nuclear factor-kappa B (NF-κB) and mitogen-activated protein kinases (MAPKs)[32,33].

The NLRP3 inflammasome represents a crucial link between oxidative stress and neuroinflammation. Activation of NLRP3 by ROS and amyloid-beta promotes the release of IL-1β and IL-18 while facilitating tau pathology and neuronal damage. Specialized microglial

populations with enhanced lipid accumulation and ROS production have also been identified as important contributors to neurodegenerative progression[32,33].

7.1 Interaction Between Oxidative Stress and Neuroinflammation

Oxidative stress and neuroinflammation form a self-perpetuating cycle in dementia pathogenesis. Elevated ROS levels stimulate inflammatory signaling and microglial activation, while activated microglia generate additional ROS through NOX enzymes and mitochondrial dysfunction. This vicious cycle exacerbates synaptic damage, neuronal loss, and cognitive impairment, thereby accelerating disease progression[34,35].

7.2 Therapeutic Implications and Challenges

Given the close relationship between oxidative stress and neuroinflammation, therapeutic strategies targeting both pathways simultaneously may provide significant clinical benefits. Antioxidants such as glutathione, vitamin E, and coenzyme Q10, as well as NOX inhibitors, have demonstrated neuroprotective effects in preclinical studies by reducing oxidative damage and inflammatory responses[36].

However, translating these findings into effective clinical therapies remains challenging due to difficulties in achieving adequate blood-brain barrier penetration, target specificity, and optimal treatment timing. Current research focuses on modulating microglial activation states, enhancing mitochondrial quality control mechanisms, and selectively inhibiting pathological ROS generation. Novel compounds possessing both antioxidant and anti-inflammatory properties, combined with efficient brain delivery systems, represent promising therapeutic approaches for slowing neurodegeneration and preserving cognitive function in dementia[36].

8. Cholinergic Hypothesis and Neurotransmitter Dysregulation

Dementia, particularly Alzheimer's disease (AD), remains one of the most prevalent neurodegenerative disorders characterized by progressive cognitive decline and memory impairment. Among the various theories proposed to explain its pathogenesis, the cholinergic hypothesis is one of the earliest and most extensively studied. This hypothesis suggests that degeneration of cholinergic neurons in the basal forebrain and the consequent reduction in acetylcholine (ACh) neurotransmission contribute significantly to the cognitive deficits observed in dementia. However, contemporary evidence indicates that cholinergic dysfunction represents only one component of a broader network of neurotransmitter abnormalities involved in disease progression[37–39].

8.1 Cholinergic Dysfunction in Dementia

Acetylcholine is a critical neurotransmitter involved in learning, memory, attention, and cognitive processing. Cholinergic neurons originating primarily from the nucleus basalis of Meynert project extensively to the cerebral cortex, hippocampus, and amygdala, regions that are essential for cognitive function. In Alzheimer's disease, progressive degeneration of these neurons results in reduced choline acetyltransferase (ChAT) activity, decreased acetylcholine synthesis, and impaired cholinergic neurotransmission. These changes contribute directly to memory deficits and cognitive decline[37–39].

Cholinergic signaling is mediated through two major receptor families: muscarinic acetylcholine receptors (mAChRs) and nicotinic acetylcholine receptors (nAChRs). Among nicotinic receptors, the α4β2 and α7 subtypes are particularly important for cognitive function. Reduced expression of these receptors has been documented in Alzheimer's disease. The α7 nicotinic receptor is of special interest because it exhibits high affinity for amyloid-beta peptides. Under physiological conditions, activation of α7-nAChRs promotes synaptic plasticity and memory formation; however, pathological interactions with amyloid-beta impair receptor function and contribute to neuronal toxicity and synaptic dysfunction[37–39].

The balance between acetylcholine synthesis, receptor activation, and degradation is significantly disrupted in dementia. Increased acetylcholinesterase (AChE) activity accelerates the breakdown of acetylcholine within synaptic clefts, further reducing cholinergic signaling. This understanding forms the basis for the use of acetylcholinesterase inhibitors such as donepezil, rivastigmine, and galantamine, which remain among the few approved symptomatic treatments for Alzheimer's disease. Nevertheless, their clinical benefits are generally modest and temporary, highlighting that restoration of acetylcholine levels alone is insufficient to reverse the complex neurochemical alterations associated with dementia[37–39].

8.2 Neurotransmitter Dysregulation Beyond Acetylcholine

Dementia involves dysfunction of multiple neurotransmitter systems beyond the cholinergic pathway. Noradrenergic neurons located within the locus coeruleus undergo early degeneration during Alzheimer's disease progression, resulting in impaired norepinephrine signaling. Since norepinephrine regulates attention, arousal, stress responses, and cognitive flexibility, disruption of this system contributes substantially to cognitive impairment and behavioral symptoms. Regional variations in adrenergic receptor expression further influence the severity and pattern of cognitive deficits observed in affected individuals[37–39].

Glutamatergic neurotransmission is also profoundly altered in dementia. Glutamate serves as the principal excitatory neurotransmitter within the central nervous system and plays a critical role in synaptic plasticity, learning, and memory. Dysregulation of glutamate signaling, particularly through N-methyl-D-aspartate (NMDA) receptors, contributes to excitotoxicity, neuronal injury,

and synaptic loss. Excessive activation of NMDA receptors leads to intracellular calcium overload, oxidative stress, mitochondrial dysfunction, and ultimately neuronal death. These mechanisms provide the rationale for the use of memantine, an NMDA receptor antagonist, in the management of moderate-to-severe Alzheimer's disease[37–39].

8.3 Interactions Among Neurotransmitter Systems

Neurotransmitter systems within the brain function as highly interconnected networks rather than isolated pathways. Cholinergic signaling interacts closely with glutamatergic, dopaminergic, serotonergic, and noradrenergic systems to regulate cognition and behavior. Nicotinic acetylcholine receptors, for example, modulate NMDA receptor activity within the hippocampus and prefrontal cortex, thereby influencing synaptic plasticity and memory formation. Disruption of these interactions leads to widespread neural circuit dysfunction, contributing to progressive cognitive decline, behavioral abnormalities, and impaired executive functioning[37–39].

Consequently, dementia should be viewed as a disorder involving global neurotransmitter dysregulation rather than a disease caused solely by cholinergic deficiency. Understanding these complex neurochemical interactions may facilitate the development of more effective multitarget therapeutic strategies aimed at preserving cognitive function and slowing disease progression[37–39].

9. Vascular Contributions and Comorbidities

The pathophysiology of dementia is multifactorial and extends beyond neurodegenerative mechanisms alone. Although Alzheimer's disease pathology remains central to many dementia syndromes, growing evidence demonstrates that vascular abnormalities play a crucial role in cognitive decline. Vascular contributions to cognitive impairment and dementia (VCID) encompass a broad spectrum of cerebrovascular disorders that may independently cause dementia or interact synergistically with neurodegenerative processes to accelerate disease progression[40].

9.1 Cerebral Small Vessel Disease and Vascular Dementia

Cerebral small vessel disease (cSVD) is one of the most significant vascular contributors to cognitive impairment and represents a major cause of vascular dementia. This condition affects the brain's small arteries, arterioles, capillaries, and venules, leading to structural and functional vascular abnormalities. Common pathological features include arteriolosclerosis, lipohyalinosis, microatheroma formation, and cerebral amyloid angiopathy (CAA), all of which contribute to vessel wall thickening, luminal narrowing, impaired cerebral perfusion, and chronic ischemic injury[41].

Persistent cerebral hypoperfusion resulting from cSVD leads to white matter damage, neuronal dysfunction, and progressive cognitive decline. Executive dysfunction, impaired attention, slowed information processing, and reduced cognitive flexibility are among the most prominent clinical

manifestations. Unlike Alzheimer's disease, memory impairment may initially be less pronounced, while deficits in executive function and processing speed often predominate[41].

Neuroimaging studies commonly reveal characteristic features of cSVD, including white matter hyperintensities (WMHs), lacunar infarcts, cerebral microbleeds, and enlarged perivascular spaces. These lesions accumulate gradually over time and disrupt neural connectivity within critical cognitive networks. As a result, communication between cortical and subcortical brain regions becomes increasingly impaired, contributing to progressive cognitive deterioration[41].

Importantly, cerebral small vessel disease frequently coexists with Alzheimer's disease pathology. The presence of both vascular and neurodegenerative abnormalities gives rise to mixed dementia, a condition associated with greater cognitive impairment and more rapid disease progression than either pathology alone. This overlap complicates diagnosis, prognosis, and therapeutic management, emphasizing the need for comprehensive evaluation of both neurodegenerative and vascular risk factors in patients presenting with cognitive decline[40,41].

9.2 Vascular Dysfunction Mechanisms

Dementia-related vascular dysfunction is a multifaceted process involving several interconnected mechanisms that contribute to cognitive decline and neurodegeneration[42,43].

Hypoperfusion and Hypoxia

Narrowing and stiffening of cerebral small vessels reduce blood flow to the brain, resulting in chronic cerebral hypoperfusion. Deep white matter regions and watershed zones are particularly vulnerable because of their limited collateral blood supply. Reduced cerebral perfusion impairs oxygen and nutrient delivery, leading to mitochondrial dysfunction, oxidative stress, and progressive neuronal injury, thereby contributing to cognitive impairment and neurodegeneration[42,43].

Blood–Brain Barrier Disruption

The blood–brain barrier (BBB) plays a critical role in maintaining cerebral homeostasis by regulating the exchange of substances between the bloodstream and brain tissue. In cerebral small vessel disease (cSVD) and vascular dementia, endothelial dysfunction, pericyte loss, and chronic inflammation compromise BBB integrity. Increased permeability permits the entry of harmful plasma proteins, inflammatory mediators, and immune cells into the brain parenchyma, exacerbating neuroinflammation and neuronal damage[42,43].

Chronic Inflammation

Persistent low-grade vascular inflammation is a major contributor to dementia pathology. Activation of endothelial cells and perivascular macrophages promotes the expression of adhesion molecules, facilitating leukocyte infiltration into brain tissue. Pro-inflammatory cytokines,

including interleukin-1β (IL-1β) and tumor necrosis factor-alpha (TNF-α), sustain a chronic inflammatory environment that accelerates vascular injury, synaptic dysfunction, and neuronal loss[42,43].

Impaired Interstitial Fluid and Glymphatic Clearance

The glymphatic system is responsible for the removal of metabolic waste products and toxic proteins from the brain. In vascular cognitive impairment, disruption of perivascular drainage pathways impairs glymphatic function, leading to the accumulation of neurotoxic proteins and metabolic by-products. This process contributes to white matter injury, neurodegeneration, and progressive cognitive decline[42,43].

9.3 Cardiovascular Comorbidities Exacerbating Dementia

Several cardiovascular and metabolic disorders significantly increase the risk of vascular cognitive impairment and dementia by promoting cerebrovascular dysfunction and neurodegeneration[44].

Hypertension

Hypertension accelerates arterial wall remodeling, increases oxidative stress, and impairs neurovascular coupling, resulting in dysregulated cerebral blood flow. Long-standing uncontrolled hypertension is considered one of the strongest modifiable risk factors for cerebral small vessel disease and dementia[44].

Diabetes Mellitus

Diabetes mellitus contributes to microvascular damage, endothelial dysfunction, chronic inflammation, and prothrombotic states. These alterations adversely affect cerebral circulation and increase the risk of cognitive decline and dementia[44].

Atrial Fibrillation

Atrial fibrillation increases the risk of cerebral microemboli and ischemic strokes, many of which remain clinically silent. Repeated vascular insults progressively disrupt neural networks and accelerate cognitive deterioration[44].

Obesity and Smoking

Obesity and cigarette smoking promote vascular inflammation, oxidative stress, endothelial dysfunction, and atherosclerosis. These factors collectively impair cerebrovascular health and contribute to the development and progression of dementia[44].

9.4 Mixed Pathologies and Dementia Progression

Vascular lesions frequently coexist with Alzheimer's disease pathology, including amyloid-beta plaques and neurofibrillary tangles. The coexistence of vascular and neurodegenerative abnormalities results in mixed dementia, which is associated with more severe cognitive impairment and a faster rate of disease progression than either pathology alone. Vascular injury

lowers the threshold for clinical dementia expression by impairing cerebral perfusion, disrupting neuronal connectivity, and amplifying neuroinflammatory responses[45].

9.5 Therapeutic Implications

Current management strategies focus primarily on aggressive control of vascular risk factors, including optimal blood pressure management, lipid regulation, antiplatelet therapy when indicated, smoking cessation, regular physical activity, and dietary modification. These interventions can slow vascular injury and reduce the risk of cognitive decline[46].

Emerging therapeutic approaches aim to target vascular inflammation, restore blood–brain barrier integrity, improve endothelial function, and enhance glymphatic clearance. Advances in neuroimaging and biomarker development are also facilitating earlier detection of vascular pathology, enabling intervention before the onset of significant cognitive impairment. Early diagnosis and comprehensive management of vascular risk factors remain essential for preventing or delaying dementia progression[46].

10. Limitations of Conventional Therapies

Current Pharmacological Options

Alzheimer's disease (AD) and related dementias remain significant therapeutic challenges, as currently available conventional treatments provide only modest symptomatic benefits without substantially altering disease progression[47,48].

The primary pharmacological therapies approved for AD include cholinesterase inhibitors (ChEIs), namely donepezil, rivastigmine, and galantamine, as well as the N-methyl-D-aspartate (NMDA) receptor antagonist memantine[47,48]. ChEIs enhance cholinergic neurotransmission by inhibiting acetylcholinesterase, thereby increasing synaptic acetylcholine levels and improving cognitive function. Memantine acts by modulating glutamatergic neurotransmission through NMDA receptor blockade, reducing excitotoxic neuronal damage associated with AD pathology[47,48].

Donepezil is widely prescribed for mild-to-moderate AD and provides modest improvements in cognition and global clinical outcomes. Rivastigmine is approved for mild-to-moderate AD and Parkinson's disease dementia, with demonstrated benefits in cognition and activities of daily living. Galantamine additionally modulates nicotinic acetylcholine receptors, which may enhance attention and executive function. Memantine is indicated for moderate-to-severe AD and can be administered alone or in combination with ChEIs to improve cognition, behaviour, and daily functioning[47,48].

Aducanumab, developed by Biogen, received accelerated approval from the United States Food and Drug Administration (FDA) in 2021 due to its ability to reduce amyloid-beta plaque burden.

Unlike symptomatic therapies, aducanumab targets a key pathological hallmark of AD. However, its clinical efficacy remains controversial because reductions in amyloid burden have not consistently translated into meaningful cognitive benefits. Several additional immunotherapeutic agents targeting amyloid-beta and tau proteins are currently under investigation, although definitive disease-modifying effects have yet to be established[47,48].

Adverse Effects and Tolerability Issues

The clinical utility of conventional dementia medications is frequently limited by adverse effects that compromise patient adherence and long-term treatment success[49].

Cholinesterase inhibitors commonly cause gastrointestinal adverse effects, including nausea, vomiting, diarrhoea, anorexia, and weight loss. These adverse reactions are among the leading causes of treatment discontinuation. Rivastigmine, particularly in its oral formulation, is associated with a higher incidence of gastrointestinal intolerance, whereas transdermal patch formulations demonstrate improved tolerability and reduced gastrointestinal symptoms[49].

Memantine is generally better tolerated but may cause dizziness, headache, confusion, constipation, and fatigue. Combination therapy with memantine and donepezil may offer greater symptomatic benefits than monotherapy but can also increase the incidence of adverse events, thereby affecting treatment acceptability[49].

Monoclonal antibodies such as aducanumab are associated with amyloid-related imaging abnormalities (ARIA), including cerebral oedema and microhaemorrhages. Consequently, patients receiving these therapies require regular neuroimaging surveillance and careful clinical monitoring[49].

Management of behavioural and psychological symptoms of dementia using antipsychotic medications is similarly challenging because these agents are associated with increased risks of cerebrovascular events, mortality, sedation, and metabolic complications, particularly in elderly individuals[49].

10.1 Limited Disease-Modifying Potential

One of the greatest limitations of current dementia therapies is their inability to significantly alter the underlying neurodegenerative process[50].

Although cholinesterase inhibitors and memantine can temporarily improve cognitive symptoms and quality of life, they do not prevent neuronal loss, halt disease progression, or reverse existing neuropathological changes. Consequently, patients continue to experience progressive cognitive decline and functional deterioration despite ongoing treatment[50].

Disease-modifying approaches targeting amyloid-beta and tau pathology have generated considerable interest; however, clinical outcomes have been mixed. Several therapeutic agents have successfully reduced amyloid burden yet failed to demonstrate substantial improvements in cognition, daily functioning, or overall disease progression. Furthermore, these therapies are often

most effective when administered during the earliest stages of disease, limiting their applicability in routine clinical practice[50].

Similarly, beta-secretase and gamma-secretase inhibitors designed to reduce amyloid-beta production have produced disappointing clinical results due to limited efficacy, unacceptable toxicity, or worsening cognitive outcomes during clinical trials[50].

The multifactorial nature of AD, involving amyloid accumulation, tau pathology, oxidative stress, neuroinflammation, mitochondrial dysfunction, vascular injury, and synaptic impairment, presents a major obstacle to the development of effective single-target therapies. Consequently, contemporary treatment strategies remain largely symptomatic while research continues to explore combination therapies and multi-target approaches capable of slowing or preventing disease progression[50].

10.2 Economic and Accessibility Challenges

The implementation of conventional dementia therapies is further complicated by substantial economic and accessibility barriers[51–53].

The financial burden of dementia extends beyond medication costs and includes expenses associated with hospitalization, long-term care, specialist consultations, diagnostic evaluations, caregiver support, and productivity losses. Cost-effectiveness analyses suggest that cholinesterase inhibitors and memantine may be economically beneficial under specific circumstances; however, affordability remains a significant challenge for many healthcare systems and patients[51–53].

Access to dementia treatment is particularly limited in low- and middle-income countries (LMICs), where healthcare resources, diagnostic infrastructure, and specialist services are often insufficient. Many patients are unable to obtain regular treatment because of medication costs, inadequate healthcare coverage, and shortages of trained healthcare professionals capable of providing ongoing monitoring and management[51–53].

The burden is further amplified by indirect costs associated with informal caregiving. Family members frequently provide extensive unpaid care, resulting in financial strain, reduced workforce participation, emotional stress, and diminished quality of life. In many settings, these indirect costs exceed direct medical expenditures yet remain inadequately recognized within healthcare policies and reimbursement frameworks[51–53].

Geographical barriers, limited healthcare infrastructure, low health literacy, and inadequate awareness of dementia further restrict access to diagnosis and treatment. Rural populations and underserved communities are particularly affected by these disparities, resulting in delayed diagnosis and reduced access to available therapies[51–53].

Moreover, conventional pharmacological models often fail to account for cultural, social, and socioeconomic factors that influence treatment adherence and healthcare utilization. Effective dementia management requires not only medications but also robust healthcare infrastructure,

patient education, caregiver support, and long-term monitoring systems, which remain unavailable in many resource-constrained settings[51–53].

In summary, conventional dementia therapies are limited by modest efficacy, adverse effects, lack of disease-modifying potential, high costs, and substantial accessibility barriers. These challenges highlight the urgent need for affordable, accessible, and innovative therapeutic approaches capable of addressing the growing global burden of dementia across diverse populations and healthcare systems[51–53].

10. Herbal Nootropics: Definition and General Characteristics

Herbal nootropics are naturally occurring compounds derived from plants that possess cognitive-enhancing properties, including improvements in memory, attention, learning, and overall cognitive performance. The term "nootropic," derived from the Greek words *nous* (mind) and *tropein* (to bend or turn), was first introduced by Giurgea in 1972 to describe substances capable of enhancing higher integrative brain functions, particularly learning and memory. Herbal nootropics constitute a distinct subclass of nootropics because they originate from medicinal plants and contain bioactive phytoconstituents that contribute to their therapeutic effects.

Several medicinal plants have traditionally been used to support cognitive performance, brain health, and neuroprotection. Common examples include *Bacopa monnieri*, *Ginkgo biloba*, *Centella asiatica* (Gotu kola), *Panax ginseng*, and *Salvia officinalis* (sage). These herbs are particularly attractive because they exert multiple therapeutic effects rather than acting through a single neurotransmitter system. Their mechanisms include antioxidant activity, neurotransmitter modulation, enhancement of cerebral blood flow, and promotion of neurotrophic signaling pathways involved in learning and memory processes[54, 55].

Herbal nootropics possess complex phytochemical profiles composed of flavonoids, terpenoids, saponins, alkaloids, and other bioactive constituents that contribute to their cognitive-enhancing properties. However, many of these compounds are polar and water-soluble, which may limit their bioavailability by reducing their ability to cross lipid-rich biological membranes. To overcome these limitations, advanced formulation technologies such as phytosomes, which complex plant extracts with phospholipids, have been developed. Phytosome formulations improve solubility, stability, gastrointestinal absorption, and overall bioavailability of herbal constituents, thereby enhancing therapeutic efficacy.

Although growing evidence supports the effectiveness of herbal nootropics, their benefits generally emerge following long-term administration rather than acute use. This delayed onset is attributed to their ability to modulate physiological processes and promote neuroprotection rather than simply providing immediate symptomatic relief. Nevertheless, further clinical studies are required to establish their pharmacokinetic characteristics, optimal dosing regimens, and long-term safety profiles.

In summary, herbal nootropics represent a promising class of agents for promoting brain health, combining the traditional wisdom of herbal medicine with modern pharmacological approaches. They offer potential benefits for cognitive enhancement, neuroprotection, reduction of oxidative stress, and healthy aging, although challenges such as limited blood-brain barrier penetration and delayed onset of action remain. Continued advances in formulation technologies and clinical research are expected to further strengthen their therapeutic potential[56,57].

10.1 Advantages Over Synthetic Drugs

Herbal nootropics offer several advantages over synthetic cognitive enhancers and neuroprotective agents. Unlike many synthetic drugs that act through a single molecular target, herbal nootropics contain multiple bioactive compounds that may act synergistically to improve cognitive function. This polypharmacological approach provides broader therapeutic effects by targeting multiple pathological processes, including oxidative stress, inflammation, neurotransmitter imbalance, and neuronal degeneration.

Another important advantage is their generally favorable safety profile. Serious adverse reactions are relatively uncommon compared with many synthetic pharmaceuticals. Although improper use, contamination, or misidentification may still pose risks, herbal medicines are widely perceived as safer alternatives due to their long history of traditional use and lower incidence of severe side effects.

Herbal nootropics also tend to support physiological homeostasis rather than inducing strong pharmacological effects. Through their antioxidant, anti-inflammatory, neurotrophic, and neuromodulatory activities, these agents may enhance the body's natural protective mechanisms while minimizing toxicity. This integrated mode of action contrasts with the more targeted but sometimes disruptive effects of synthetic drugs.

Accessibility and affordability further contribute to their appeal. Many herbal nootropics are available without prescription and have been used for centuries in traditional healthcare systems worldwide. Their widespread availability enables broader public access, although issues related to quality control and standardization remain significant concerns.

Despite these advantages, herbal nootropics also have limitations. Their pharmacokinetic properties can be variable because herbal preparations often contain numerous active constituents. In addition, long-term clinical evidence regarding efficacy and safety remains less robust than that available for many synthetic medications. Nevertheless, their multitarget actions, favorable tolerability, and therapeutic versatility continue to support growing interest in their application for cognitive enhancement and neuroprotection[58–60].

10.2 Regulatory and Standardization Issues

Despite their therapeutic promise, herbal nootropics face substantial regulatory and standardization challenges that affect their clinical acceptance and safe use. Unlike synthetic drugs, herbal products

contain complex mixtures of bioactive compounds whose composition can vary according to plant species, geographical origin, cultivation practices, harvesting conditions, and extraction methods. This variability makes it difficult to establish consistent standards for identity, purity, potency, and quality.

Classification of herbal nootropics also varies considerably across different countries. Depending on national regulations, these products may be categorized as dietary supplements, herbal medicines, traditional remedies, or functional foods. Such inconsistency creates regulatory gaps and complicates the implementation of uniform safety and efficacy standards. Consequently, products containing similar ingredients may be subjected to markedly different regulatory requirements across jurisdictions.

Product adulteration and contamination present additional concerns. Herbal products may contain undeclared synthetic substances, cheaper substitute materials, heavy metals, pesticide residues, or microbial contaminants. Furthermore, environmental factors such as temperature, humidity, and light exposure can adversely affect product stability and quality.

To address these issues, modern quality-control technologies including chromatographic phytochemical profiling, DNA barcoding, and Good Agricultural and Collection Practices (GACP) have been introduced. However, these approaches require specialized expertise and substantial financial resources, limiting their widespread implementation, particularly in low-resource settings. Although pharmacopeial monographs can provide standardized specifications for individual herbs, global harmonization remains limited.

The absence of internationally harmonized regulations poses challenges for manufacturers, especially small and medium-sized enterprises that must comply with differing requirements across markets. Strengthened collaboration among regulatory agencies, researchers, healthcare professionals, and industry stakeholders is therefore essential to establish common standards that ensure the safety, efficacy, quality, and consistency of herbal nootropics.

In summary, regulatory and standardization issues remain major barriers to the broader clinical adoption of herbal nootropics. Addressing these challenges will require continued scientific investigation, regulatory harmonization, resource allocation, and international cooperation to ensure that the therapeutic potential of these natural cognitive enhancers can be safely and effectively realized[61–63].

10.3 Prominent Herbal Nootropics Studied in Dementia

Herbal nootropics have gained substantial attention in dementia research because of their multitarget pharmacological actions and comparatively favorable safety profiles. Numerous medicinal plants, particularly those originating from Ayurvedic, Traditional Chinese, and other traditional medical systems, have been investigated for their potential to improve cognitive

function, reduce neurodegeneration, and alleviate symptoms associated with dementia, including Alzheimer's disease[64, 65].

Herbal Nootropic	Key Active Constituents	Botanical Source
Ashwagandha	Withanolides, steroidal lactones	Withania somnifera
Turmeric	Curcumin, turmerones	Curcuma longa
Brahmi (Bacopa monnieri)	Bacosides A & B, triterpenoid saponins	Bacopa monnieri
Shankhapushpi	Triterpenoids, flavonoids	Convolvulus pluricaulis
Gotu Kola	Asiatic acid, madecassoside, triterpenoids	Centella asiatica
Ginkgo biloba	Flavonoids, terpenoids	Ginkgo biloba
Panax ginseng	Ginsenosides	Panax ginseng
Huperzia serrata	Huperzine A	Huperzia serrata

Botanical Name: *Withania somnifera*
Common Name: Ashwagandha
Genus and Family: Genus: Withania
Family: Solanaceae
Parts Used: Mostly the roots but also the leaves are used Roots are the most commonly used part in both traditional and modern usages.

About the Plant

Ashwagandha is a stout, erect, branching shrub, with a central stem and covered with wooly hairs; its extensive medicinal use in Ayurvedic system of medicine have been mentioned in the Ayurvedic literature. Dubbed the “Indian ginseng,” it is revered for its life-giving properties. Its name means 'smell of horse', alluding to the traditional weapon that is clearly thought to impart the strength and virility of a stallion. This plant is not taken for one disease but as a general support, particularly around physical and mental strength. This baby’s been used for three millennia

Active Constituents

The miracle compounds of Ashwagandha are primarily found in withanolides, a group of steroidal lactones. The main compounds are withaferin A, withanone, and withanolide A; they have a multi-target effect on various biological pathways providing a strong antioxidant, anti-inflammatory, and neuroprotective activity. They also contribute to cellular stress maintenance by inducing the expression of heat shock proteins and promoting clearance of misfolded proteins.

Neuroprotection in Dementia

One such herb that has excited people is Ashwagandha which has been labeled as a herbal nootropic for dementia. Both clinical and preclinical studies suggest it can enhance memory, attention and cognitive processing speed, especially in cases of mild cognitive impairment. It works through a variety of mechanisms: clearing up the toxic amyloid-beta plaques in the brain that's associated with Alzheimer's, increasing brain-derived neurotrophic factor (BDNF) and promoting neuron growth, protecting against oxidative stress, and reducing inflammation in the brain. Ashwagandha also blocks the acetylcholinesterase enzyme and can also help increase acetylcholine levels in the brain that are critical for memory. The evidence is strong in models and early human trials, but more large clinical trials are required to verify its complete role in dementia.

Mechanism of Action

Ashwagandha acts on multiple fronts. It blocks the pathways that lead to inflammation and oxidative stress those are what cause neuronal death in dementia. Its withanolides stimulate the body to make more of its own antioxidants, enhancing cellular defense. Inhibits the breakdown of acetylcholine, an important neurotransmitter for memory and learning processes. It also modulates the immune response in the brain, soothing microglia and sweeps toxic protein aggregates like amyloid-beta out of brain tissue.

Botanical Name: *Centella asiatica*

Common Name: Pennywort, Gotu Kola

Genus and Family: Genus:Centella

Family: Apiaceae

Parts Used: Primarily leaves but also aerial parts/occasionally roots.

About the Plant

Pennywort is a creeping herbaceous perennial plant commonly growing in tropical and subtropical climates, in damp shady areas. It's been used in traditional Asian medicine, particularly Ayurveda and traditional Chinese medicine, for a couple thousand years as a memory enhancer, blood purifier and wound healer. It's frequently referred to as a "brain tonic" because it is thought to revitalize and reconstruct nerve cells, enhance cognitive functions and reduce anxiety.

Active Constituents

The plant has an abundant source of pentacyclic triterpenoids including asiaticoside, madecassoside, asiatic acid and madecassic acid as a major bioactive compounds. Asiaticoside and madecassoside are particularly powerful in their ability to enhance collagen synthesis, preserve neuronal protection, and regulate oxidative stress involved in the regulation of cognitive function.

10. Neuroprotection in Dementia

Centella asiatica has been demonstrated by several studies to enhance cognitive function, learning and memory particularly in animal models of Alzheimer's disease and dementia. It is believed to work by blocking acetylcholinesterase, which in turn boosts levels of acetylcholine necessary for

memory and learning. The plant extracts also shielded neurons from amyloid-beta toxicity, a hallmark of dementias. It also lowers oxidative stress and inflammation in the brain two of the primary reasons for neurodegeneration. While human clinical trials are in their early stages, preliminary research indicates that Centella asiatica may have potential associations with improved cognitive performance and mood among elderly individuals and those with mild cognitive impairment.

Mechanism of Action

Centella asiatica has a pleiotropic action. It turns on the NRF2 pathway, a master regulator of antioxidant response that cranks up detoxifying enzymes that guard brain cells. It blocks acetylcholinesterase, boosting levels of acetylcholine dousing the brain in crucial neurotransmitters for cognition. The triterpenoids also exert anti-inflammatory effects through inhibition of NF-κB, as well as proinflammatory cytokines such as TNF-α and IL-6. It also enhances the function of mitochondria, supporting brain cells as they generate energy in an efficient manner. It helps break the vicious cycle of neuronal death in dementia by lowering oxidative stress and inflammation, while also stimulating neurogenesis

Botanical Name: *Ginkgo biloba*
Common Name: Ginkgo, Maidenhair Tree
Genus and Family: Genus: Ginkgo
Family: Ginkgoaceae
Parts Used: The Leaves, mainly leaves although part of the bark and seeds are used too based on the extract, but mainly it in the extracts.

About the Plant

Ginkgo biloba is a living fossil species of tree, native to China and known for millennia. This herb has been a staple in traditional medicine for centuries in East Asia and is now known worldwide for its stimulating effects. Frequently known as a "dementia hopeful leaf," Ginkgo is uniquely capable of both regulating blood flow and protecting itself from external stressors, which in turn translates into benefits for the brain and heart.

Active Constituents

The primary bioactive constituents include isoflavones (quercetin, kaempferol, and isorhamnetin) and terpene lactones (ginkgolides A, B, C, and bilobalides). These phytochemicals have antioxidants, anti-inflammatory and neuroprotective effects. Ginkgolides prevent platelet-activating factors, a substance with effects on the circulation of blood and inflammation. The free radical scavenging ability of flavonoids prevents neurons from oxidative damage.

Neuroprotection in Dementia

Ginkgo biloba is the subject of many studies looking at how it helps with dementia, especially for people with Alzheimer's and vascular dementia. It enhances cognitive abilities such as memory,

attention and executive processing. In Alzheimer's models, Ginkgo biloba also reduces amyloid-beta plaque and neurofibrillary tangle aggregations, the associated key pathologies, by slowing down neurodegeneration. It also affects neurotransmitter systems, such as acetylcholine, amplifying brain signaling that is critical for memory. Clinical trials demonstrate that treatment with formulated Ginkgo extracts (such as EGb 761) leads to an enhanced cognition and reduced neuropsychiatric symptoms in dementia patients, which may be even similar or synergistic effects compared to conventional drugs. Current and future studies are still determining the ideal dose and long-term effects, but Ginkgo is one of the best natural nootropics for brain aging and staving off dementia.

Mechanism of Action

Ginkgo operates on so many fronts. First, it's a powerful antioxidant. Prevents free radicals from attacking brain cells. Then, it suppresses platelet activating factor, enhances microcirculation and increases blood supply to the brain. This can reduce hypoxia and keep the neurons healthy. It's also protective of the mitochondria, our energy factories in cells, which frequently go awry in dementia. The terpene lactones inhibit the excitotoxicity from excessive glutamate and reduce neuron death. The flavonoids and terpenoids inhibit pathways that lead to inflammation, reducing cytokines that exacerbate brain injury. It also modulates neurotransmitters such as dopamine and acetylcholine, when enhancing the brain's communication. [70–72]

Botanical Name: *Bacopa monnieri*

Common Name: Brahmi, Water Hyssop

Genus and Family: Genus: Bacopa
Family: Plantaginaceae

Parts Used: The whole herb including the leaves and stem are used in extracts and traditional medicine.

About the Plant

Bacopa monnieri is a perennial, creeping herb mostly found in wetlands and muddy shores in Asian countries, particularly in India. Described more than 1400 years ago in Ayurveda, it is considered as one of the best natural brain tonics known as a Medhya rasayana that helps in enhancing memory and intellect. It is ingested in teas, capsules or powders.

Active Constituents

The powerful neuroactive substances are bacosides A and B, bacopasaponins, alkaliods including brahmine, and flavanoids as quercetin. These compounds have been demonstrated to possess antioxidant, anti-inflammatory and anti-apoptotic properties. Bacosides specifically activates neuronal synthesis, kinase activity, and synaptic function. Its neuroprotection is multifunctional, as other components such as betulinic acid, asiatic acid and loliolide also participate in it. The saponins and triterpenoid components contribute to attenuating oxidative stress, inflammation, and mitochondrial dysregulation.

Neuroprotection in Dementia

Bacopa monnieri is one such exception as there is significant evidence backing up its nootropic and neuroprotective properties about dementia and Alzheimer's. It enhances memory, attention and executive function by various mechanisms. It is involved in the regulation of neurotransmission, synaptic plasticity and neurogenesis. Bacosides block pro-inflammatory cytokines such as TNF-α, and IL-6 while preventing toxic neuroinflammation. It decreases the accumulation of amyloid-beta plaques and hyperphosphorylation of tau proteins which are characteristic traits in the Alzheimer's disease donepezil reduce. Bacopa clinical trials support the ability of this substance to increase cognition and mood in both MCI and dementia patients, with a good safety profile. It also controls the signaling cascades in apoptosis, protein misfolding, and neuroendocrine activities, thereby providing an all-around protective role.

Mechanism

It's kind of multi-pronged. First, Bacopa holds back acetylcholinesterase the enzyme that breaks down acetylcholine, so more acetylcholine hangs around to help memory. Second, bacosides decrease brain inflammatory cytokines such as TNF-α and IL-6-mediated neuroinflammation. Third, the antioxidants sweep up free radicals that damage neurons by oxidative stress. Fourth, it activates signaling pathways that fix and grow nerve connections and support the energy metabolism of brain cells. So, Brahmi works by preventing neurons from dying, reconnecting brain cells and soothing inflammation

11. Botanical Name: *Huperzia serrata*
Common Name: Chinese Club Moss
Genus and Family: Genus: Huperzia
Family: Lycopodiaceae

Parts Used: Entire plant is used long-traditionally, however for extract the aerial portion and leaves are most commonly used.

About the Plant

Huperzia serrata is a fern native to Eastern Asia, found in China, Tibet, from Japan to Korea. Historically it was used for memory loss, psychosis, inflammatory conditions and injury. The actual active magic ingredient here is huperzine A, a naturally occurring alkaloid found in this plant that has received enormous attention around the world for its potential in treating cognitive disorders such as dementia and Alzheimer's disease.

Active Constituents

The major component of the drug is Huperzine A, an alkaloid which is chemically classified as a sesquiterpene tetracyclic with a highly complex structure. It functions primarily as a powerful, reversible and selective inhibitor of acetylcholinesterase (AChE), which basically means that it stops the enzyme responsible for breaking down acetylcholine an important neurotransmitter

required for memory and cognition. Beyond this, antioxidant and anti-inflammatory effects and a rescue of neurons from apoptosis (cell death) have been reported as well as multiple neuroprotective pathways including those related to mitochondria, amyloid precursor protein metabolism and nerve growth factors.

Neuroprotection in Dementia

The huperzine A from *Huperzia serrata* is a promising herbal nootropic that uplifts cognition primarily by raising acetylcholine in the brain. It crosses the blood-brain barrier effectively, which is what makes it potent relative to a lot of medications. Huperzine A protects neurons against the toxic effects of β-amyloid, reduces levels of oxidative stress, and blocks apoptosis by modulating anti-apoptotic proteins. It also boosts the signaling of nerve growth factors and supports synaptic plasticity, enabling brain cells to grow literally to sprout new appendages and connect with one another better. But longer-term studies and broader testing are still needed to fully confirm its benefit and safety.

Mechanism of Action

Huperzine A is an acetylcholinesterase (AChE) inhibitor that increases acetylcholine critical to memory and learning. It also acts on NMDA receptors, which decreases excitotoxicity that is said to be neuronal death. These phenolic acids and other chemicals all help quell NF-kB activation so inflammation is lowered. Plus, it protects mitochondria themselves, halting the energy crisis in those defective brain cells. Most importantly, it enhances signaling in the ERK pathway, which benefits nerve cells and enables them to survive and repair

Active Constituents

Curcumin is the principal bioactive polyphenolic compound in turmeric, structurally identified as 1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione. It is associated with other curcuminoids, demethoxycurcumin and bisdemethoxycurcumin. These compounds have potent antioxidants and anti-inflammatory properties. They alter various signaling pathways contributing to oxidative stress, inflammation, mitochondria function and amyloid plaque formation which are important for dementia. Volatile oils and the essential vitamins present in turmeric also play a part in its health benefits. The use of nanoparticles, phytosomes and co-administration with piperine has been found promising in clinics.

Neuroprotection in Dementia

Neuroprotective effects of curcumin in dementia are well established using animal models and from the preliminary clinical studies. It attenuates oxidative stress, by scavenging ROS and enhancing endogenous antioxidant enzymes such as glutathione and superoxide dismutase. It also inhibits neuroinflammation by reducing pro-inflammatory cytokines, including TNF-α, IL-1 and IL-6, and inflammasome activation.

This multitarget effect leads to robust memory spatial learning and cognitive behavior improvement in several dementia rodent models, including those produced by amyloid-beta,

streptozotocin or high-fat diets. Curcumin suppresses amyloid aggregation and hyperphosphorylation of tau protein, ameliorating the pathological characteristics of AD. In addition, it replenishes synaptic proteins, as well as improves neuronal survival, to contribute to the homeostasis of brain plasticity.

Though the low natural bioavailability of curcumin hindered clinical translation, new formulations such as lipid nanoparticles and curcumin-phosphatidylcholine complexes significantly increase its brain delivery and efficacy. Some studies have seen cognitive improvement as well as less inflammation in elderly patients with mild cognitive impairment or dementia. The favorable safety profile of curcumin makes it a potentially suitable adjunctive target agent for prevention and treatment of dementia.

Mechanism

Curcumin acts in many ways. It clogs enzymes that help to form plaque. It activates the Nrf2 pathway, something of a master antioxidant switch, calling on the body to ratchet up its defenses in cells. It checks NF-kB – the inflammation king. And then there's the mitochondrial modulation by curcumin, which boosts energy production and guards against cell death. Moreover, it regulates brain chemicals that are crucial for a good memory. So, essentially, curcumin fights oxidation, blocks inflammation (the molecular basis of diabetes and all the most common diseases), is said to fight cancer (as well as preventing it) and keeps neurons alive

Active Constituents

The major active components are sesquiterpenoids, especially jatamansone (also known as nardostachone), valeranone, and isovalerenic acid. These components are responsible for their anxiolytic, sedative and neuroprotective properties. It also harbours alkaloids, flavonoids and essential oils which are responsible for its medicinal values. The components of EA were studied for synergistic mechanism to calm the nerve conduction, to alleviate the peroxidative stress and to promote neural regeneration, respectively.

13. Neuroprotection in Dementia

Nardostachys jatamansi has promising potential as an herbal nootropic that may reduce cognitive decline and enhance brain health in dementia sufferers. Its neuroprotective properties are related to control of oxidative stress and neuroinflammation, both contributory determinants for developing dementia. The compounds of the plant also act as inhibitors of the enzymes responsible of oxidative injury and reductor signals that support pro-inflammatory cytokines, and they are able to protect neurons under damage.

Studies proved that Spikenard promotes neurogenesis, facilitates synaptic plasticity and keep neuronal int integrity. The growth factor can induce the neurotrophic factor for nerve growth and regenerate demyelination. In animals, it has been demonstrated to increase memory and reduce anxiety while shielding against amyloid plaque related neurodegeneration.

Although human data are scarce, initial observations indicate *Nardostachys jatamansi* may be a valuable addition to the management of dementia patients, acting as both neuroprotective and cognition-sparing agents by virtue of its calming effects, antioxidant properties and ability to promote brain rejuvenation.

Mechanism of Action

The mechanism seems multi-model. First, its antioxidant molecules hunt down free radicals shielding neurons from damage. Second, it blocks enzymes involved in the inflammation process and suppresses cytokines such as TNF-α. Third, it increases brain chemicals like dopamine and serotonin, creating positive mood effects as well as positive cognitive ones. Fourth, it supports mitochondrial function, keeping neurons energized and healthy. Finally, it is thought that it may block cholinesterase, increasing acetylcholine levels which are essential for memory.

So, in simple terms Spikenard preserves nourishes and repairs the brain cells. It's also an ancient remedy with potential to slow dementia's progression and perhaps help improve memory a natural multitasker for brain health

Animal models in Dementia Research

Animal-based models are essential for dementia studies. They allow us to understand the disease and screen potential treatments before going into humans. The complexity of the brain (and its associated symptoms) does not always translate directly into these models. But they are our best weapons right now.

Scopolamine-Induced Dementia Model

The scopolamine-induced model is one of the mostly used models. Scopolamine is a drug that inhibits the activity of acetylcholine, a neurotransmitter that plays a key role in memory. Injected, it rapidly leads to memory loss and cognitive deficits in rodents. These effects bear some similarity to aspects of dementia, particularly Alzheimer's disease.

While the memory deficits are short term, it is wonderful for quick drug screening of substances that might bolster cognition. It also replicates other features such as oxidative stress, mitochondrial impairment and neuroinflammation present in brains of people with dementia. But keep in mind that scopolamine doesn't kill neurons, so it is not the end of the story

Toxin-Based Models

To simulate Parkinsonian and certain dementias neurodegeneration models, toxins like MPTP, 6-hydroxydopamine(6-OHDA)- or rotenone-are introduced.

- MPTP is specific in that it kills only dopamine-producing neurons, causing motor and cognitive dysfunction resembling Parkinson's dementia. But animals tend to recover, at least partially, over time, making them less ideal for modeling long-term dementia.
- 6-OHDA produces selective damage to the dopaminergic pathways and is used as a tool for investigating memory and attention deficits.

- Rotenone makes Lewy body like pathology with aggregation of alpha-synuclein and neuroinflammation, so Rotenone better imitates the progress of Parkinson's dementia.

These models of toxins are valuable for studying mechanisms of neurodegeneration, but do not always reproduce the range of the disease

Transgenic Animal Models

In the era of genetics, animal models have been produced in which transgenic animals express mutated human genes associated with familial dementia. This includes mice harboring:

- Pathogenic mutations in APP and PSEN1/2 leading to amyloid-beta deposits,
- Neurofibrillary tangles consisting of hyperphosphorylated mutated tau proteins,
- Alpha-synuclein (mutated) - For Lewy body dementia.

These animals' manifest gradual neurodegeneration, synaptic deficit and cognitive loss that more closely mirror human disease. But the studies typically target rare familial forms of dementia, not the most common age-related sporadic Alzheimer's

Preformed Fibril Models

Even more recently, misfolded alpha-synuclein, preformed fibrils (PFF) have been injected into rodents. This makes the protein diffuse and aggregate again, resembling more organic disease development of cognitive symptoms

Behavioral Tests in Models

In animal models, cognitive features are assessed through mazes and recognition tests:

- Spatial memory is measured in the Morris Water Maze.
- Y-Maze tests working memory.
- Recognition memory was assessed using Novel Object Recognition.
- Fear Conditioning measures associative memory.

Behavior in animals can be influenced by motor deficits or anxiety, so data require cautious interpretation. [87,88]

Limitations and Perspectives

No animal model can replicate human dementia in its entirety. They all reflect on some aspects of the disease neurotransmitter deficits, protein aggregation, inflammation or neuron loss. When researchers tie multiple models together from the effects of acute toxins to chronic genetic epigenetics.

In addition, cross-species and high complexity of human brain were barriers to translate. Yet, these are irreplaceable models when combined with cellular and computational approaches using human cells to translate into treatment for the dementia

13. Preclinical Studies of Herbal Nootropics

Animal studies serve as a critical foundation for preclinical dementia research and provide an effective platform for evaluating the therapeutic potential of herbal nootropics. Among the various experimental models, the scopolamine-induced dementia model is widely used because it mimics cholinergic dysfunction and memory impairment characteristic of the early stages of Alzheimer's disease. Scopolamine blocks acetylcholine receptors, resulting in deficits in learning and memory. Numerous plant-derived compounds, including polyphenols, alkaloids, and terpenoids, have demonstrated the ability to reverse scopolamine-induced cognitive impairment while reducing oxidative stress and neuroinflammation.

Polyphenolic compounds such as quercetin and resveratrol exert neuroprotective effects by scavenging reactive oxygen species and enhancing endogenous antioxidant defense systems, including superoxide dismutase (SOD) and catalase (CAT). Flavonoids have also been shown to upregulate brain-derived neurotrophic factor (BDNF), thereby promoting neurogenesis and synaptic plasticity. Alkaloids such as huperzine A, isolated from *Huperzia serrata*, act as potent acetylcholinesterase inhibitors, increasing synaptic acetylcholine levels and improving neurotransmission involved in learning and memory. In addition, huperzine A exhibits anti-inflammatory and anti-apoptotic properties that contribute to neuronal protection. Terpenoids derived from medicinal plants such as ginseng and turmeric suppress inflammatory pathways, including nuclear factor-kappa B (NF-κB), and reduce the production of pro-inflammatory cytokines such as TNF-α and interleukins. These compounds may also improve mitochondrial function and support neuronal energy metabolism. Furthermore, combinations of herbal constituents often produce synergistic effects by simultaneously targeting cholinergic dysfunction, oxidative stress, neuroinflammation, and protein aggregation associated with dementia pathology. Behavioral assessments such as the Morris Water Maze (MWM), Y-maze, and Novel Object Recognition (NOR) test are commonly employed to evaluate improvements in spatial memory, working memory, and recognition memory following administration of herbal extracts. Collectively, preclinical evidence indicates that herbal nootropics target multiple pathogenic mechanisms involved in dementia and therefore represent promising candidates for further therapeutic development[90].

13.1 Overview of Clinical Studies and Meta-Analyses

Clinical investigations of herbal nootropics have demonstrated encouraging results, although many studies remain limited by relatively small sample sizes and short treatment durations. Among the most extensively studied herbal agents, *Ginkgo biloba* has consistently shown modest but significant improvements in cognitive function, activities of daily living, and neuropsychiatric symptoms in patients with mild-to-moderate dementia. Several meta-analyses have confirmed the safety and efficacy of standardized *Ginkgo biloba* extracts, particularly EGb 761.

Curcumin supplementation has also demonstrated potential benefits through its anti-inflammatory and antioxidant properties, with some studies reporting improvements in cognitive performance and reductions in biomarkers associated with neurodegeneration. However, its clinical utility remains limited by poor bioavailability, prompting the development of novel formulations designed to enhance absorption and therapeutic efficacy.

Combination therapies involving herbal nootropics alongside approved anti-dementia medications have shown additive cognitive benefits and improved tolerability in several studies. Meta-analytic evidence suggests that herbal nootropics may serve as valuable adjunctive therapies in dementia management. Nevertheless, large-scale, high-quality randomized controlled trials employing standardized outcome measures are still required to establish definitive clinical recommendations.

Overall, both preclinical and clinical evidence suggests that herbal nootropics act through multiple neuroprotective pathways and may provide symptomatic and supportive benefits in dementia management with relatively few adverse effects. Future research should focus on identifying optimal formulations, dosing strategies, and long-term therapeutic outcomes[91,92].

14. Challenges in Translating Animal Data to Clinical Practice

Animal studies remain indispensable in dementia research; however, translating preclinical findings into clinical success remains challenging. Although rodent models provide valuable mechanistic insights, they do not fully replicate the complexity of human dementia. Most experimental models rely on toxin-induced injury or genetic modifications that rapidly produce pathological features, whereas human dementia develops gradually over decades through complex interactions among aging, genetics, environmental exposures, and metabolic factors.

Differences in pharmacokinetics, metabolism, and physiology further complicate translation. Doses that are safe and effective in animals may not produce comparable outcomes in humans, and adverse effects may differ substantially across species. Additionally, many preclinical studies are limited by small sample sizes, inadequate controls, and methodological bias, reducing their predictive value for clinical efficacy.

Even advanced transgenic models expressing human Alzheimer's disease-associated genes fail to fully reproduce the complete spectrum of human pathology. While these models may develop amyloid plaques or tau tangles, they often lack the extensive neuronal loss and progressive neurodegeneration observed in patients. Consequently, therapeutic interventions that appear successful in animal studies frequently fail to demonstrate meaningful clinical benefit in human trials.

Another limitation is the difficulty of modeling the prolonged preclinical phase of dementia within the relatively short lifespan of laboratory animals. No existing animal model perfectly captures the complexity of human disease. Therefore, future research should integrate animal studies with

human cell-based models, computational approaches, biomarker-driven investigations, and improved clinical trial designs to enhance translational success.

Despite these challenges, animal research remains essential for understanding disease mechanisms and identifying potential therapeutic targets. Continued refinement of experimental models and translational methodologies will be critical for advancing effective dementia therapies from bench to bedside[93,94].

15. Future Directions and Challenges

A. Need for Standardized Extracts and Dosing

One of the major challenges associated with herbal medicines is the lack of standardization. Extracts derived from the same plant species may exhibit substantial variations in their phytochemical composition due to differences in cultivation conditions, harvesting time, processing methods, and storage practices. Consequently, establishing standardized protocols for extract preparation, quality control, and dosage determination is essential. Without such standardization, clinical outcomes remain inconsistent, research findings become difficult to reproduce, and healthcare professionals face challenges in recommending evidence-based therapies. The development of validated quality standards and dosing guidelines is therefore critical for the successful integration of herbal nootropics into dementia management strategies[95].

B. Lack of Large-Scale Multicenter Clinical Trials

Although numerous studies have investigated the cognitive benefits of herbal nootropics, most clinical trials remain limited by small sample sizes, short durations, and single-center designs. Such limitations reduce the generalizability of findings and restrict the ability to evaluate long-term efficacy and safety. Dementia is a heterogeneous and slowly progressive disorder that requires large, multicenter, randomized controlled trials involving diverse patient populations. Well-designed international studies are necessary to establish robust clinical evidence, facilitate regulatory approval, and support widespread clinical adoption of herbal therapies. Increased research funding and global collaboration will be essential to address these gaps and advance the field[96,97].

C. Herb–Drug Interactions and Safety Monitoring

The increasing use of herbal supplements alongside conventional medications has raised important concerns regarding herb–drug interactions, particularly among older adults with dementia who frequently receive multiple medications. Many herbal constituents can influence drug-metabolizing enzymes, transport proteins, and neurotransmitter systems, potentially altering the efficacy or safety of prescribed treatments. Despite these concerns, systematic monitoring and reporting of herb–drug interactions remain inadequate. Comprehensive pharmacovigilance

systems, improved patient education, routine safety assessments, and interdisciplinary healthcare coordination are required to ensure the safe and effective use of herbal nootropics in clinical practice. Further research is needed to better characterize these interactions and establish evidence-based safety recommendations[98,99].

D. Integrative Approaches and Combination Therapies

Dementia is a multifactorial disorder involving numerous pathological mechanisms, including neuroinflammation, oxidative stress, protein aggregation, mitochondrial dysfunction, and neurotransmitter deficits. Consequently, single-target therapies often provide limited clinical benefit. Herbal nootropics possess multiple bioactive constituents capable of acting on several pathological pathways simultaneously and may therefore complement conventional pharmacological treatments. Combination therapies that integrate herbal medicines with standard anti-dementia drugs may enhance therapeutic efficacy, improve symptom control, and reduce adverse effects. However, such approaches require careful formulation, rigorous clinical evaluation, and individualized treatment planning to avoid unwanted interactions and maximize therapeutic outcomes. The development of evidence-based integrative treatment strategies represents a promising yet challenging frontier in dementia care that will require close collaboration among clinicians, researchers, pharmacologists, and regulatory authorities[100,101].

15.Conclusion

Dementia is a multifactorial neurodegenerative condition driven by interconnected mechanisms including amyloid-beta accumulation, tau hyperphosphorylation, oxidative stress, neuroinflammation, mitochondrial dysfunction, cholinergic deficits, and vascular impairment. Current pharmacological therapies provide modest symptomatic relief but fail to substantially alter disease progression. Their limited disease-modifying potential, adverse effects, accessibility issues, and high economic burden highlight the urgent need for safer, multi-target, and affordable therapeutic strategies.

Herbal nootropics represent a promising complementary approach in dementia management. Unlike single-target synthetic drugs, botanical agents such as *Bacopa monnieri*, *Ginkgo biloba*, *Withania somnifera*, *Curcuma longa*, *Centella asiatica*, and *Huperzia serrata* demonstrate multi-modal mechanisms. These include acetylcholinesterase inhibition, antioxidant and anti-inflammatory actions, modulation of neurotransmitters, mitochondrial protection, improved cerebral circulation, and enhancement of neurotrophic factors such as BDNF. Preclinical evidence consistently supports their neuroprotective and cognition-enhancing properties, while emerging clinical studies suggest modest but meaningful cognitive benefits, particularly when standardized extracts are used.

However, significant challenges remain. Variability in phytochemical composition, lack of standardization, limited large-scale randomized controlled trials, potential herb–drug interactions,

and regulatory inconsistencies restrict widespread clinical adoption. Translation from animal models to human application also remains complex due to biological heterogeneity and methodological limitations.

Future research should prioritize standardized formulations, rigorous multicenter clinical trials, pharmacokinetic profiling, and integrative therapeutic models combining herbal and conventional strategies. With scientific validation and regulatory refinement, herbal nootropics may evolve from supportive supplements to evidence-based adjuncts in comprehensive dementia care.

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