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Herbal Nootropics in Dementia: Pathways of Neuroprotection and Cognitive Recovery

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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 act on a 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 standardisation and large-scale trials restricts 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 nobody knows it. Like, the brain is on strike. Dementia According to World Health Organization (WHO), dementia is an ailment which comes up because of neurodegenerative process in brain, frequently chronic sometimes progressive disease. Patients lose bunches of brain things, such as memory, thinking, learning, language, calculation and judgment along with comprehension just about life lost inside mind. It comes primarily after fifty but can come at any age, mainly after 50. Among the causes may be genetics, stroke, age, infection or even physical problems with the body's handling of liver, kidney and vitamin B12: the body offers up on the brain. But the brain doesn't just forget, the

brain works very hard to keep us from remembering how freaked out it was the last time. Only now you can't seem to remember anything else. Your brain won't let this go and now you know why: because your workplace is terrible and on fire, basically. And because in 2020 even thinking clearly is a diagnosable problem that causes real harm, prevents even easy things from being done properly or easily or right at all, all lost beneath layers of lawyer-ese justification imposed by idiot face-baring kill enabling graphic designers who apparently refuse to wear shoes with laces. At various times are delirious, dream incoherently, cannot tell what is right or wrong. These types of dementia patients also smile one time, are angry there and then weep for no reason at other times.

Dementia is characterized by a progressive, global, and irreversible decline of cognitive abilities as well as memory, reasoning, and behaviour. It's not just forgetting. It's all the loss in the brain. No memory, no thought, language eluded him. No judgment. Diagnosis is made using laboratory testing, neuroimaging investigation such as MRIs, with history and symptomology all used in clinical practice. Although some types are reversible with treatment, they are often progressive and disabling. And the thought, the memory, the speech it's all chaos. It's such an awful decline that the patient is a dependent, can't even feed themselves.

Dementia and delirium are not the same, don't get them confused. Delirium comes quickly, improves quickly; dementia comes slowly, worsens slowly. Occasionally, dementia appears in tandem with other conditions, including depression or problems with movement. Dementia not just memory loss, it's like everything is lost. [1]

2.Classification of Dementia

There aren't even enough categories for brain because dementia is so varied. Dementia Classification: Dementia is classified in many ways:

2.1Anatomical Classification

- **Cortical Dementia:** It attacks the outer layer in the brain and cerebral cortex that looks after higher level of thinking. Memory encoding, aphasia (inability to use language), agnosia & apraxia (loss of the ability to recognize objects or process language) and abstraction problems are the symptoms. MEMORY - Memory can often be attributed to a storage failure. Alzheimer, Frontotemporal, Creutzfeldt-Jakob Disease are correlative diseases.
- **Subcortical Dementia:** Subcortical is the term that describes this dementia of which the areas that are inferior to the cortex like white matter, thalamus, brainstem and basal ganglia being more affected. Symptoms may include an inability to concentrate, difficulties with speed of thought (bradyphrenia), movement problem, problems in 'executive' areas of thinking (problems related to planning, organisation and sequencing) and mood changes. Memory deficits are often retrieval-based. Associated diseases are Parkinson, Huntington, Vascular and Progressive Supranuclear Palsy.

2.2 Classification based on Etiopathogenesis

- **Reversible Dementia:** This is caused by the causes which can be rectified or normalized by treatment. It is usually acute or sub-acute, in relation to metabolic shortage, infectious process or toxic agents. Cognitive problems are associated with inattention, slow processing and mild to moderate memory impairment which can be remedied by treatment of the cause. For Example: Hypothyroid Dementia, Drug induced dementia and many more.
- **Permanent Loss of Dementia:** Permanent dementia is the progressive loss of cognitive function that cannot be fully undone, or reversible. It's generally sneaky and long-term. Cognitive abnormalities such as aphasia, visuospatial decline and executive function modestly concurrent to severe memory loss. Example: Alzheimer, Huntington.

2.3 Clinical and Neuropsychological Spectrum

- **Alzheimer Disease:** AD is the most common amnestic neurodegenerative disorder that develops insidiously. Attributed to accumulation of β-amyloid plaques, neurofibrillary tangles and reduction in acetylcholine due to atrophy of basal forebrain. Cognitive disturbances such as episodic memory loss (Fowler); impairment of vision perception as well as confusion about time and lack of apathy.
- **Vascular Dementia (VaD):** A type of dementia that occurs when the blood supply to the brain is reduced which can lead to damage and death of brain cells. This lowered blood flow might be the result of a stroke, vessels clot or bleeding in brain. Notable Differences Decline in executive function, slowed thinking and difficulty concentrating Less severe memory problem but associated with multiple behavioral and physical symptoms including mood swings, depression, balance problem, numbness and urinary urgency.
- **Mixed Dementia:** It is the coexistence of two or more types of dementia in an individual. The most frequent ones are Alzheimer and vascular dementia. As we age, this takes place multiple pathological process can occur in the brain simultaneously that can exacerbate the cognition decline more than any one individual condition may induce.
- **Frontotemporal Dementia:** A neurodegenerative disorder with onset in the presidium period and characterized by memory impairment, early changes in personality, periods of confusion, poor judgement or loss of organizational skills, decline in language functions with preservation of social or economic activity. It occurs because of abnormal build-up of proteins such as tau, TDP-43 and FUS. Finally, cognitive sequelae that may occur include impaired executive functioning, linguistic deficits and poor decision-making as well as emotional numbing and loss of social propriety.
- **Dementia with Lewy Bodies:** The second most common forms of dementia due to abnormal buildup of alpha-synuclein, lewy bodies in the cortex and brain stem that affects thinking, behaviour, alertness, & movement. Clinical features involve cognitive

fluctuations (fluctuations in the level of attention and alertness), visual hallucination, bradykinesia, fewer history of tremor and REM sleep behaviour disorder. [2,3]

3. Historical Perspective

Avicenna made categories a long time ago some variation of memory loss, thinking problems, image problems. He said; and it is three kinds: Fisad-al-Zekr (memory lost), Fisad-al-Fekr (wrong judgment), Fisad-al-Takhayol (imagination lost). That seems awfully like how modern medicine classify Alzheimer's, frontotemporal, Lewy body dementia. He also penned the causes including head injury, fever, vitamin trouble, organ failure a thousand years ago sans MRI. [4]

3.1Consensus and Emerging Classification: Contemporary consensus (such as VICCS, DSM-5) now incorporates terms such as mild and major vascular cognitive impairment, post-stroke dementia being a subtype. The diagnostic criteria are evolving to more of a 'spectrum' approach rather than strict categories. [5]

3.2 Global Epidemiology of Dementia

Dementia has become one of the leading causes of death and disability in the world." It is growing quickly, like a river flood. Currently, there are 57 million people living with dementia on planet, by 2050 predictions claim it will affect 153 million people which is threefold growth. Ten million new cases occur every year. Japan, Italy, Germany and China are experiencing the high prevalence. But the problem is not limited to rich countries, with new statistics now showing that low and middle countries are starting to see numbers rise as well, particularly in parts of Asia and Africa.

Old age is the greatest risk, but dementia affects more women than men. Female-to-male ratio is approximately 1.7 at death where women outlast but sometimes pay price in dementia. Those numbers, in Japan's rapidly aging society where nearly 27 percent of its almost 130 million people are over 65, have forced the country to drown under the demand for dementia care. And the age-standardized rates are hardly moving since 1990, which according to their methods means risk factors for dementia haven't shifted just that we have old people everywhere now.

Dementia brings co-morbidities as well: diabetes, hypertension, obesity, smoking, loneliness. Some areas have stable rates; some are rising and others falling. Africa is surging fastest, but in poor countries many cases are not counted and vanish into darkness without ever being found. There are massive, massive regional differences, but every region is sitting around going. [6–8]

4.Socioeconomic Burden of Dementia

"It doesn't just ruin brains," says McKhann, "it ruins families and whole economies." The financial burden is like an iceberg: The explicit costs appear to be manageable, but the massive hidden impact remains below the surface. Using the value-of-statistical-life (VSL) approach,

the global economic cost of dementia was estimated to be $2.8 trillion in 2019 and projected to increase to $17 trillion by 2050.

For a decade, direct costs, like hospital care, nursing homes and medications have been increasing annually. But the indirect costs loss of productivity, mental stress, a hit to self-esteem and the unpaid work of family caregivers have been largely ignored. For many families there is financial destruction, and the emotional toll may be too high, all when they are busy taking care of their loved one. Family provides most dementia care, and they are also unpaid while paid caregivers suffer physical strain and anxiety.

Dementia is the most costly and burdensome medical condition in the world, but funding for dementia research by health systems lags far behind other diseases. Government cannot keep pace with accelerating disaster in a resource constraint, feeble policy adaption and encroaching global challenge.

Every site takes on the weight differently. Dementia is a strain on long-term care systems and the resources of health care budgets in wealthier countries. Most dementia patients in low-income countries never receive a diagnosis or professional care; nearly all the caregiving burden falls to their family members. Some upper middle-income countries such as China, India and Brazil are emerging as significant contributors to the global economic cost. Over two-third dementia patient will be community-dwelling in by 2050. But a lack of investment in health-care facilities means societies are ill-equipped to deal with the dementia cases that lie ahead. Thus, dementia is an emerging worldwide challenge that demands carefully coordinated and swift action. It's not just a medical burden; it's an economic and social burden as well.[9,10]

4.1 Limitations of Current Treatment

Current therapy (not really therapy, just hold hand while patient falls). Drugs against dementia such as donepezil, galantamine, rivastigmine, memantine may delay forgetting few months but symptomatic not cure of disease. This may be because the very strong blood-brain barrier that drugs cannot cross, cannot repair neurons once they are broken. So, the higher dose is what they give but this time (risk) is more for nausea, vomiting, headache or tiredness." Yet brain kills itself, patient keeps getting worse, all treatments are temporary.

Drugs good in early stage, but it comes late after brain much gone. Also, shit doesn't permeate into brain right because of shitty bioavailability. Most of clinical trials of new drugs for dementia fail. Amyloid plaques can effectively be dissolved in the brain by drugs, and yet patients hardly or never benefit clinically. Magic injections Even the much-hailed new immunotherapies so-called "magic injections" have given only modest results. Hospitals are charging increasingly while families watch the loved one die.

Non-pharmacological strategies such as regular exercise, a healthy diet and socialisation may offer some optimism even though the evidence remains inconclusive. According to research, prevention is where it's at but the process is complicated and you must be at it for decades, something not many are willing in wait out. [11]

4.2 The Need for Alternatives

The world needs better ideas such as soft nanoparticles, nanoliposomes and exosomes. These small carriers can pass through complex biological barriers, transport drugs to the location of brain lesions, and specifically induce therapy against diseased neurons. Such may play a role as the future of dementia therapy and as such we do wish to view this through liposomes, microneedle and the exosomes, but not with too many side effects or too high costs. Nonetheless, unsure as they are, scientists still hope for more. New, simpler and safer methods for drug delivery to the brain with less loss of the drug are also necessary.

Genetic therapies, gene editing and antibody-based treatments are also making progress, though they are uncertain and staggeringly expensive. Alternatives such as dietary interventions, omega-3 supplements, lifestyle changes and cognitive training may provide a better option but it's just not easy quickly enough for the few. The reality is that an old-new combination of drugs, diet, exercise and technology could be the appetite for the future challenge. Any delay could be disastrous. There is no time for institutions to weigh the future, and families should not have to endure the mounting injury. [12]

5. Introduction to Nootropics

Nootropics otherwise known as smart drugs, sometimes ancient herbs or simply vitamins. They go to them hoping their brain won't work so much, that they won't lose their memory, that they'll be able to hang on to a thought. But in neurodegenerative diseases, the loss of brain function is a brutally concrete thing, and glacially slow and inevitable. There is no magic cure. Slowly the brain slips away and there is simply nothing doctors can do but watch, as even the best medicines bring only partial relief and can't slow down the slide. [13]

5.2 The Growing Relevance of Nootropics

Nootropics are getting more popular these days. They were available in the form of plants, lab-made synthetic ones and came with everyday foods. Young and old, ailing and healthy alike, student or non-student, all desire better memory with focus of thought and negligible scope of forgetfulness. Now, whether they're natural or man-made doesn't seem to matter. They could be a very useful tool for neurodegenerative diseases, and with usually severe or no side effects. That hope, it gives them relevance.

Diseases such as Alzheimer, Parkinson and other brain conditions steadily kill off neurons. Yet during this carnage nootropics looks like a saviour for not only neuroprotection, but further enhance memory, learning and quality of life. Herbs like Bacopa, Ginkgo, Ashwagandha, Ginseng are all conducted repeatedly. Some have a role to play in antioxidant pathways, some in anti-inflammatory pathways and some give hope through faith. Synthetic options, such as Piracetam and other racetams, work on neurotransmitters and some may assist in cognition, though the evidence is not clear.

Although scientific papers and clinical trials continue to mushroom, but their results are sometime strong and eventually weak as well. In some cases, benefits emerge only in animals and not humans. But people keep trying. The age-old traditional systems of medicine including

Ayurvedic and Chinese always propagated brain tonics and now the modern medical science is in its quest to discover and demystify it. Polyherbal extracts and their mixes touch many pathways in the brain simultaneously, and that multitargeting could be their greatest benefit. (14,15)

5.3Mechanistic Perspective

The mechanism of nootropic isn't that simple since they also work on multiple pathways simultaneously. Some lower oxidative stress, some soothe inflammation or function as antioxidant. They might also see to it that mitochondria stay healthier for a longer duration. Nootropic also alter certain neurotransmitters such as acetylcholine, dopamine and help to prevent neurons from damage due to toxic proteins like amyloid, tau, alpha synuclein. Some also enhance blood flow in brain. Some even help gut microbiome, so brain-gut axis have benefit too. In addition, some of the Indian herbs as *Withania somnifera*, *Bacopa monnieri* and *Curcuma longa* has exhibited multitargeted approach rather than showing single action.

Artificial nootropics like piracetam primarily target neuron cell membranes, neurotransmitter release modulating, ion channels changing. The latter should allow an integrated and more holistic level of support for brain operation that is multilevel. (16,17)

5.5 Historical Perspective on Nootropics

Nootropics are basically the brain booster or memory pills and also called as smart drugs. Science has fancy terms for them but there's nothing complicated about their underlying idea. It's nothing new that people have a desire for better thinking, for more memory and less foggy brain. For that, students eat almonds at breakfast, too; it's why Greeks used to stick rosemary in their hair once upon a time for sharp thinking; and now everyone hopes there is some pill out there that will do the trick. People are doing cognitive enhancement of some sort always. Today it is big business but also real hope for people suffering cognitive decline.

The general idea is this: if it enhances aspects of brain function (such as learning and memory) that are important to you, then it's a nootropic. The word 'nootropic' was first used by C.E.Giurgea in 1972, the name is derived from Greek words "noos" meaning mind and "tropein" meaning turn. (The Greek "nous" means "mind," so nootropic originally meant something like "turn mind," or make it better. It should aid in learning, promote stress-resistant brains, shield from toxins and not be sedating and have limited side effects. Finally, it must be effective in both the healthy and diseased brain. These drugs be it herbs, or chemical, or nutrient is meant to treat conditions like Alzheimer's and ADHD and dementia, but healthy people. They raise acetylcholine, glutamate, dopamine, blood flow or battle-free radicals. Sometimes no one even knows how it works. Nevertheless, many made good use of them as they feel its effects for real people. (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 risks. [19]

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

Mechanism of Cognitive Enhancement with Nootropics

Nootropics for the brain's helpers. They do more than wake you up; they tweak, tune and perhaps protect the brain. But they do so in a highly complicated manner: They don't work in a single way but instead through multiple mechanisms, including many chemicals and different pathways of the brain.

Mechanisms

Cognition Enhancement Nootropics work primarily by modulating neurotransmitters, increasing metabolism in the brain, and protecting neurons from injury.

1. **Neurotransmitter Modulation:** A lot of nootropics enhance the action of ACh through inhibition of acetylcholinesterase (AChE), which means better memory and learning. On the other side, drugs such as methylphenidate improve attention and working memory through increasing dopamine and noradrenaline in PFC – that also modulate reasoning, focus and motivation. Several more work via glutamate receptors (NMDA, AMPA), enhance synaptic plasticity and long-term potentiation (LTP), which are important in memory formation and learning.
2. **Improved Energy Metabolism:** Certain nootropics enhance the provision of energy to neurons by improving glucose metabolism and mitochondrial function. Take piracetam, for example, which improves membrane fluidity and enhances mitochondrial energy production in aging brains that allow neurons to operate more healthily.
3. **Neuroprotection:** Nootropics have antioxidant and anti-inflammatory properties, thus they protect neurons from oxidative stress and excitotoxicity. This decelerates the damage from aging or neurodegeneration. Some decrease buildup of toxic proteins such as amyloid beta, which has been connected to Alzheimer's, preserving synaptic function.
4. **Neuroplasticity and Synaptic Function:** Nootropics support brain by increasing synaptic density, modulating receptor function, promoting neurogenesis. Increased expression of brain derived neurotrophic factor (BDNF) and nerve growth factor (NGF) has been evidenced along some natural nootropics such as panax ginseng and

curcumin, both pivotal for the proper development of neurons; particularly in stacking with a racetam.

5. **Vascular Effects:** Better cerebral circulation is a second mechanism as certain herbal substances (Ginkgo biloba) are vasodilators promoting better oxygen and nutrient supply to key regions of the brain. [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

Pathophysiology of Dementia

Dementia is a clinical syndrome characterized mainly by cognitive deterioration that can result from several pathological processes. Neuro Metabolic Disorder is largely responsible for most of dementias including Alzheimer's disease (AD), the neurodegenerative metabolism forms are not normal, and protein metabolism disorder plays an important part. The hallmark of neurodegenerative processes causing dementia is the accumulation and crosstalk between abnormal amyloid-beta (Aβ) peptides and tau protein. [26]

Neurodegenerative Mechanisms

The different mechanisms of neurodegeneration are described as follows:

Amyloid-Beta Pathology

Amyloid Precursor Protein (APP) is a transmembrane glycoprotein that plays an important role in the neuro-cut acid balance, and its metabolism appears to be the heart of dementia pathophysiology. The two pathways that depend on the enzymes of secretase to catalyze APP proteolytic cleavage and produce Aβ peptides (primarily Aβ40 and more aggregation prone

Aβ42): The first one is the non-amyloidogenic pathway where α- and γ-secretases are used; whereas, the second one is termed amyloidogenic pathway in this case β- and γ-secretases are used. The over production of Aβ, primarily the Aβ42 isoform, that accumulate in the extracellular compartment to form soluble oligomers, fibrils and then mature senile plaques; this is due to mutation in the APP or presenilin genes (or α- β- γ-secretase dysregulation, defective clearance mechanisms).

Oligomeric species of Aβ are currently considered as the most predominantly neurotoxic forms that interferes with synaptic activity through various mechanisms (e.g., receptor modulation (N-Methyl-D-Aspartate Receptor, α 7 Nicotinic Acetylcholine Receptor), disturbances in calcium homeostasis, mitochondrial dysfunction, oxidative stress formations and inflammatory responses). For relevance is the fact that Aβ deposition sets off a series of events leading to synaptic and neuronal loss, resulting in the clinical presentation of cognitive decline. However, the association between plaque load and dementia severity is weak, suggesting that additional factors are involved in the symptomatic progression of the disease. [27,28]

Tau Protein Abnormalities

Tau, a microtubule-binding protein, is believed to play an important role in stabilizing microtubules essential for maintaining axonal transport and neuronal structure. The MAPT (microtubule associated protein tau) gene undergoes alternative splicing generating six isoforms of the tau protein, containing either three or four microtubule-binding repeats (3R and 4R), whose expression is equilibrium in adult human brains. During pathological processes, tau can be post translationally modified anomalously, especially hyperphosphorylated by kinases like glycogen synthase kinase-3 (GSK-3), cyclin-dependent kinase 5 (CDK5) and other kinases. Hyperphosphorylated tau disassociates from microtubules resulting in microtubule destabilization and accumulation of tau as paired helical filaments to create intraneuronal neurofibrillary tangles (NFTs). The NFT load correlates closely with the loss of neurons and severity of symptoms. Tau pathology develops in a predictable sequence throughout the brain and propagates trans-synaptically in prion-like fashion from the entorhinal cortex to the hippocampus and neocortex, according to disease stage and cognitive impairment. Accumulation and spreading of tau pathology not only disrupt cytoskeletal trafficking but also lead to deranged mitochondrial functions, neuroinflammation, and synaptic dysregulation. [29]

Interplay Between Amyloid-Beta and Tau

The synergy between the two proteins contributes to the neurodegeneration process, recent studies have shown. The amyloid cascade hypothesis suggests that the Aβ deposition leads to tau hyperphosphorylation and aggregation which in turn accelerates the severity of neurotoxicity. Experimental evidence also suggests that on the one hand Aβ oligomers trigger aggregation of tau while, on the other side, tau aggravates Aβ accumulation and affects synaptic pathology. The mutual interactions thereby contribute to dysregulated control of gene expression crucial for synaptic activity. Furthermore, Aβ-targeted therapies have been found to lower tau pathology and vice versa. This would indicate that a combination therapy against both these proteins can be the most efficient one to stop disease progression. [30]

Additional Pathogenic Factors

In addition to Aβ and tau, neuroinflammation (Microglial activation and cytokine release) is also strongly involved in neuronal death and synaptic loss. This feedback loop leads to an exaggerated pathology resulting from the Il and 12 responses. Genetic determinants such as apolipoprotein E4 (APOE4) allele modify both Aβ aggregation and tau pathology and affect the risk and progression of disease. Metabolic alterations, mitochondrial dysfunction and oxidative stress-induced result in an augmented global neurodegeneration.

Oxidative Stress in Dementia

The imbalance between production of reactive oxygen species (ROS) and the ability of the organism to counteract them leads to oxidative stress (OS). ROS, such as superoxide anions, hydroxyl radicals, and hydrogen peroxide (H2O2), are natural products of cellular metabolism that are predominantly produced by the mitochondria electron transport chain complexes and enzymatic sources, such as NADPH oxidase. Physiologically required at low levels for signaling, high ROS accumulation results in oxidative damage of lipids, proteins, nucleic acids as well as other cellular elements. The brain is particularly susceptible to oxidative injury because of its high rate of oxygen consumption, large number of polyunsaturated fatty acids, transition metals and relative lack of antioxidant defense systems.

Oxidative stress is an early and sustained feature in dementia that goes along with classic pathological features like amyloid-beta (Aβ) plaque aggregation and tau hyperphosphorylation. Marked elevations in oxidative damage markers, such as lipid peroxidation products (e.g., malondialdehyde), 4-hydroxynonenal, protein carbonyls, 3-nitrotyrosine and oxidized DNA/RNA bases, have been discovered in the brains, CSF and plasma of patients. ROS mediate mitochondrial dysfunction, synaptic deficits, and neuronal apoptosis in support of the degenerative cascade. Furthermore, oxidative stress also increases the activity of kinases such as glycogen synthase kinase-3 (GSK-3), leading to tau phosphorylation and consequently neurofibrillary tangle formation. [31]

7.Neuroinflammation and Microglial Activation

Neuroinflammation: an immune response of the brain to homeostatic disruption, injury or protein aggregation by glial cells - microglia and astrocytes. Microglia as intrinsic immune cells of CNS actively respond in a dynamic fashion in pathological process through transitioning to activated states and producing pro-inflammatory mediators (e.g., IL-1β, IL-6TNF-α), ROS, and chemokines conducive to establishing an inflammatory milieu. Initially the final goal of microglial activation is to eliminate pathological aggregates (either Aβ or aggregated Tau) but a sustained overactivation will eventually promote neurotoxicity, synapse and neuronal loss.

The NOX family of enzymes, particularly NOX2, represent such a primary source of microglial ROS. Microglia-induced activation of NOX2 via pattern recognition receptor (PRR), e.g., complement receptor 3 and toll-like receptor 4, catalyzes the mediated release of superoxide radicals. These ROS are not only neuro-toxic, but also act as secondary messengers

that amplify pro-inflammatory signaling cascades including nuclear factor (NF)-κB and mitogen-activated protein kinases (MAPKs) leading to exacerbation of neuroinflammation.

Nucleotide binding domain (NOD)-like receptor protein 3 (NLRP3) inflammasome being activated by ROS and Aβ, is a key intermediate in the crosstalk between oxidative stress and neuro-inflammatory process, which contributes to the production of IL-1β and IL-18 cytokines in addition to involving in tauopathy. These microglia, named LDAMs exhibit an augmented ROS generation and are stuck at the baby besom state, have emerged as players in such an inflammatory-degenerative pathway, representing also a leading-edge weapon that perhaps its misfiring possibly leads to neuron loss. [32,33]

Interaction Between Oxidative Stress and Neuroinflammation

Oxidative stress and neuroinflammation are tightly related in dementia pathogenic cycle. Elevated ROS levels activate release of inflammatory cytokine and microglia activation and in turn raising more ROS production via NOX activation and mitochondrial damage. This self-reinforcing mechanism aggravates the synaptic dysfunction, neuronal loss and exacerbates cognitive decline. [34,35]

Therapeutic Implications and Challenges

Strategies that address both processes at the same time could prove to be highly effective, since oxidative stress and neuroinflammation are interconnected. Antioxidants, including glutathione, vitamin E and coenzyme Q10 as well the NOX inhibitors have been indicated in the preclinical studies to reduce oxidative damage and neuroinflammatory response. Nonetheless, there are challenges in translating these preclinical findings to the clinic because it is difficult to target brain-specific pathways and regulate timing and dose of therapy.

New therapeutic interventions including modulation of microglial activation states, enhancement of mitochondrial quality control and specific attenuation of ROS generation at enzymatic targets such as NOX2. New investigations have now focused on compounds with anti-inflammatory and antioxidant properties that are able to cross the blood-brain barrier. [36]

Cholinergic Hypothesis and Neurotransmitter Dysregulation

Dementia, including Alzheimer's disease (AD), is still one of the most challenging neurodegenerative diseases with impairing cognitive deficits. There are diverse hypotheses related to its pathogenesis with the cholinergic hypothesis as one of the oldest and well Supported. The theory suggests that the dysfunction and death of cholinergic neurons in the basal forebrain can interfere with important cognitive functions, including memory and learning, which might lead to dementia. But it is not as simple as this cholinergic dysfunction does not exist in isolation and the neuromodulator dysregulation is more complex.

Acetylcholine (ACh) is the main transmitter of cholinergic neurons that are mainly found in the nucleus basalis of Meynert and project ACh to the cerebral cortex, hippocampus, and amygdala the areas important for cognition. These neurons degenerate and ChAT activity and ACh synthesis is reduced, leading to impaired cholinergic signaling. Yet to say that ACh alone causes dementia is precipitous; no, it's much more than that. Cholinergic neurotransmission is mediated by muscarinic (mAChRs) and nicotinic acetylcholine receptors

(nAChRs). This is also true of the nicotinic 42 and 7 types, which in AD brains display lower levels of expression. The 7-nAChR, with a high affinity for amyloid-beta, has a double duty: its normal activation being responsible for synaptic plasticity but the pathological interference of amyloid-beta with receptor function contributes to its neurotoxic role.

The equilibrium of synthesis, receptor function and breakdown (by acetylcholinesterase – AChE) are gravely disturbed in AD. Enhanced AChE activity will further limit synaptic ACh reaching the synapse, thereby augmenting cognitive deficit. Remarkably, AChE inhibitors are one of the very few approved symptomatic treatments and their effects are modest and transient. These observations indicate that elevation of the ACh level alone cannot completely reverse complicated changes in neurochemistry accompanying demential process.

Furthermore, other neurotransmitter systems--particularly the noradrenaline and glutamate systems--are heavily implicated. The noradrenergic neurons of the locus coeruleus undergo early degeneration in AD, causing modifications in norepinephrine signaling that modulate attention and arousal. Catecholamine receptors show regional differences of expression, further contributing to cognitive impairments. Similarly, impairment of glutamatergic synaptic function such as NMDA receptor deficit is an important factor causing excitotoxicity and loss of synaptogenesis in dementia.

Neurotransmitter interactions are not a simple occurrence. Cholinergic signalling reflects and is reflected by other neurotransmitter systems, e.g. nAChRs control NMDA receptor activity in the prefrontal cortex and hippocampus. An interruption of this interplay causes malfunction of all neural circuits, and consequently results in memory deficits, behavioural alterations, and dementia advances. Here, there is an abruptness the brain's hard-wired neurotransmitter network is vast and finely tuned but let one part falter and all hell breaks loose. [37–39]

Vascular Contributions and Comorbidities

The pathophysiology of dementia is a combination of multi-factorial mechanisms. Although neurodegenerative features as observed in Alzheimer's disease are central factors, over time it has become clear that vascular factors also play a key role. Vascular contributions to cognitive impairment and dementia (VCID) represent a range of cerebrovascular pathologies that impact brain function in isolation or in concert with neurodegeneration. [40]

8. Cerebral Small Vessel Disease and Vascular Dementias

Vascular contributors are cerebral small vessel disease (cSVD), affecting the brain's arterioles, small arteries, capillaries and venules. It is a leading cause of vascular cognitive impairment and dementia (VCID), the second most prevalent form of dementia after Alzheimer's disease. cSVD has a pathological expression, which includes arteriolosclerosis, cerebral amyloid angiopathy (CAA), lipohyalinosis and microatheroma. These abnormalities result in wall thickening and luminal stenosis of the vessels as well as altered cerebral blood flow. This brings an increased rate of chronic cerebral hypoperfusion, ischemia and injury to white matter along with cognitive decline (especially in domains such as executive function and attention). White matter hyperintensities (WMHs), lacunes, microbleeds, and enlarged perivascular spaces are characteristic features of cSVD on neuroimaging. These lesions slowly accrue,

ultimately disturbing the circuitry of neurons. Frequently, cSVD pathology is found in combination with Alzheimer's disease (AD) neuropathology, resulting in "mixed dementia", which further complicates the diagnosis and management of these patients. But it's not all tidy the clinical features can be insidious and move gradually, easily mistaken for something else or even just normal aging. [41]

Vascular Dysfunction Mechanisms

Dementia-related vascular dysfunction is a multifaceted process that includes the following mechanisms:

- **Hypoperfusion and Hypoxia:** Small vessel narrowing and stiffening causes decrease in blood flow to the brain. Presumptive cause is hypoperfusion of deep brain with poor response to BP change (autoregulation). The white matter and watershed zones of the brain are particularly susceptible owing to limited collateral blood supply. Reduction in perfusion leads to oxidative stress and mitochondrial impairment in neurons causing neurodegeneration.
- **Blood-Brain Barrier (BBB) Compromise:** The blood-brain barrier plays a vital role in controlling homeostasis of the brain by guarding against the passage of materials into the brain from the blood. BBB function is also disrupted in cSVD and VD through endothelial impairment, pericyte death, and inflammation. Increased BBB permeability permits deleterious plasma proteins and immune cells to penetrate cerebral parenchyma, leading to greater inflammation and brain injury.
- **Inflammation:** Chronic low-grade vascular inflammation has a major role in cSVD and dementia pathology. Endothelial cells and perivascular macrophages are activated and express adhesion molecules, allowing for infiltration of circulating leukocytes into the brain parenchyma. Cytokines such as IL-1β, TNF-α are drivers of a self-sustaining inflammatory condition that advances vascular injury and neuronal death.
- **Compromised Interstitial Fluid and Glymphatic Drainage:** Brain waste removal along the perivascular spaces are disrupted in vascular cognitive impairment. This leads to the accumulation of toxic proteins and metabolism products in brain tissue, promoting white matter damage and neurodegeneration. [42,43]

Cardiovascular Comorbidities Exacerbating Dementia

There are several comorbid settings of vascular dementia including hypertension, diabetes mellitus, obesity, smoking intolerance and atrial fibrillation that can worsen cerebrovascular pathology through some mechanisms as follows:

- Arterial wall remodeling is accelerated and oxidative stress increased; neurovascular coupling is disrupted in hypertension leading to an impairment of the regulation of CBF. Untreated hypertension is the most powerful modifiable risk for cSVD and dementia.

- Diabetes Mellitus contributes to microangiopathy and endothelial dysfunction, as well as inflammation and prothrombotic states that have detrimental effects on cerebral vasculature.
- Atrial Fibrillation poses increased risk for cerebral microemboli and ischemic strokes, the majority of which are clinically silent but become increasingly injurious to brain networks that counsel against development in brain network function because of accelerated cognitive decline.
- Obesity and Smoking amplify vascular inflammation, oxidative stress and endothelial dysfunction, adversely affecting cerebrovascular health. (44)

Mixed Pathologies and Dementia Progression

Vascular lesions are often accompanied by Alzheimer's disease (AD) pathology, including amyloid plaques and neurofibrillary tangles. This combined dementia results in a more severe cognitive impairment and a more rapid course than can be expected from either of the two alone. Vascular brain lesions reduce the threshold for clinical dementia expression by interference with delivery of oxygen and nutrients to the brain, and neuroinflammation. (45)

Therapeutic Implications

Existing therapies are based on the aggressive treatment of vascular risk factors such as blood pressure control, antiplatelet agents, lipid control and lifestyle modification (diet, exercise, smoking cessation) to slow the progression of vascular injury. New therapies such as vascular inflammation blockade, BBB recovery, and glymphatic clearance could be involved in future. Early diagnosis via advanced neuroimaging and biomarkers is essential, given that vascular pathology usually appears before symptoms.(46)

Limitations of Conventional Therapies

Alzheimer's disease (AD) and related dementias continue to represent a significant therapeutic challenge with the still numerous currently available classic treatments providing only modest improvement in symptoms. Although some medications have been approved, the restrictions related to current pharmalogical treatments are considerable and should be critically analyzed.

Current Pharmacological Options

The traditional pharmacological treatments for AD today are cholinesterase inhibitors (ChEIs) and the N-methyl-D-aspartate (NMDA) receptor antagonist memantine. Commonly used ChEIs include donepezil, rivastigmine and galantamine. These compounds primarily act by exaggerating cholinergic neurotransmission, through blocking acetylcholinesterase, with resulting increased levels of acetylcholine at the synapse. Memantine, by contrast alters the glutamate neurotransmitter system by blocking NMDA (N-methyl-d-aspartate) receptors to protect against excitotoxicity which is in turn associated with Alzheimer's neuropathology.

Donepezil is widely used in mild to moderate AD, and has some effect on cognitive function and global clinical status. Rivastigmine is indicated in AD of mild to moderate severity and in PDD with limited efficacy demonstrated on cognition and activities of daily living.

Galantamine also has nicotinic receptor modulation, which may provide added benefits on attention and executive function. Memantine is approved for the treatment of moderate to severe AD, alone or in combination with ChEIs, with demonstrated effects on cognition, behavior, and activities of daily living.

Aducanumab (Biogen) was FDA-approved in 2021 under accelerated approvals for amyloid plaque reduction, a unique approach that targets the disease pathology and not simply its symptoms. Its survival advantage remained controversial with a contrary outcome in the trials. In addition to aducanumab, other immunotherapeutic agents directed at amyloid and tau pathologies are being developed but have not demonstrated conclusive disease-modifying effect so far. [47,48]

Adverse Effects and Tolerability Issues

Conventional medicines are often constrained by adverse event profiles of treatments that, while offering symptomatic relief, can affect patient tolerability and compliance. Adverse gastrointestinal symptoms, including nausea and vomiting, diarrhea, loss of appetite are quite common with ChEIs and frequently provoke treatment withdrawal. Rivastigmine, especially when used orally, exhibits higher such adverse effect, though gastrointestinal tolerability of the transdermal patch formulation is superior with fewer reports about nausea and vomiting.

Tolerability is generally better with memantine, though dizziness, headache, confusion and constipation are side effects noted. Memantine and donepezil combination treatment, even when it is more effective than monotherapy, may have resulted in higher adverse events leading to less acceptability.

“Aducanumab and other monoclonal antibodies carry the risk of ARIA [amyloid-related imaging abnormalities] such as edema and microhemorrhages, so patients would have to undergo frequent monitoring, and patient selection would be necessary,” he added.

In addition, treatment of behavioral and psychiatric symptoms with antipsychotics is hindered by risks including mortality and cerebrovascular risk, especially in older patients with dementia. This also highlights the challenge of treating neuro-psychiatric symptoms using medications. [49]

9.Limited Disease-Modifying Potential

One of the major obstacles for current therapies is that they cannot modify the dynamic nature of Alzheimer's disease. Existing ChEIs and memantine offer relief of symptoms but do not alter the neurodegenerative processes. Even under pharmacologic treatment, patients still face progression of their cognitive and functional decline.

Immunotherapies directed against amyloid-beta and tau proteins, which are central to AD pathogenesis, bring hope for disease modifying strategies yet have only been partly successful at clinical trials. Stage so far. Some agents have been unable to translate reduction in plaque removal into significant cognitive or functional benefit. The high rates of side effects and requirement for early intervention restrict their clinical utility at present.

Moreover, phase 3 trials of beta-secretase (-secretase) and -secretase inhibitors for lowering amyloid production have had only limited success or have been disappointing, depending on the grounds considered: no efficacy or safety (toxicity, worsening cognition).

The multifaceted and intricate pathogenesis of AD, comprising amyloid, tau, neuroinflammation, oxidative stress and vascular factors impede the discovery of single-target disease-modifying therapies. Therefore, contemporary therapeutics target symptomatic management while the field actively searches for additional agents and combinatory therapies that can be leveraged in a manner to effectively stop or slow disease progression. [50]

Economic and Accessibility Challenges

Traditional interventions for dementia, which are primarily pharmacological treatments, suffer many drawbacks arising from financial constraints and accessibility. These hurdles are further complicated by the high price of drug purchase and long-term treatment, both which can be expensive in many health systems -particularly in low- and middle-income countries (LMICs). The expense of dementia care is not limited to the costs of drugs but also includes indirect costs, including caregiver burden and productivity loss to society. For instance, the cost-effectiveness studies of medications such as acetylcholinesterase inhibitors (AChEIs) and memantine show that these drugs are cost-effective only in certain situations and even then still present financial barriers to widespread use.

Moreover, the cost of these medications is high precluding access for underserved populations. Disparities in health care outcomes occur as in most of the LMICs, where most patients cannot afford regular treatment. The cost of drugs, health system constraints and a shortage of trained healthcare staff to monitor and deliver therapy also limit access to these treatments. There is thus a gap, so that the kind of available treatment is ultimately only effective in a subset of given population. The care gap is even more compounding when looking at the societal costs (including informal care) that can exceed direct medical costs yet are not well-funded or subsidized.

The barriers that lead to inaccessibility are also compounded with practical problems, including living in a rural area, limited medical facilities and poor knowledge. Numerous countries, particularly LMICs, experience challenges in distributing and sustaining adequate supplies of essential medicines. In situation without access or affordable drugs, patient will be denied for potential symptomatic relief and neuroprotection. These are the voids that illustrate the demand for affordable, available, and sustainable treatments. Such socio-economic disparities are presumably not (or hardly) addressed in our current pharmaceutical driven therapeutic model and therefore remain a serious barrier to the full-scale implementation of this therapy.

The historical focus on pharmacotherapy also overlooks the diversity in socio-economic status of various populations. Several traditional and common interventions overlook the cultural, socio-economic or social causes of therapeutic noncompliance. For medications, you need infrastructure, education and support systems that just don't exist most of the time. Thus, an

Aspirational model of care is still a theoretical ideation which fails to be applicable across diverse resource constrained regions.

In summary, the drawbacks of traditional therapies are complex. They are also prohibitively costly for both people and health systems, economically. These restrictions are even more dramatic due to issues with access, which prevent an equal distribution of treatment. Such challenges underscore the mandate for alternative, inexpensive and widely available strategies for treatment to address the burgeoning global load of dementia. Additional research and policy attention are required to narrow this treatment gap if effective treatment is to be accessible across all socio-economic strata. [51–53]

10. Herbal Nootropics: Definition and General Characteristics

Herbal nootropics are organic compounds obtained from plants with putative cognitive-enhancing features, such as memory, attention and learning influencing impact. Even the name nootropic, derived from the greek roots with meaning “mind” and tropos for means "to bend or turn”, was first used by Gieurgea (1972) to indicate substances that affect specific brain functions and that can enhance higher integrative activities of the brain, such as those related to learning ability. Herbal nootropics, being a sub-class, are unique in being of natural origin largely coming from bioactive phytoconstituents present within medicinal plants.

These natural nootropics include several plants that have long been used to help maintain, cognitive performance, brain and support neuroprotection. Some popular ones are Bacopa monnieri, Ginkgo biloba, Centella asiatica (Gotu kola), Panax ginseng and Salvia officinalis (sage). One of the reasons why these herbs are attractive is the fact that they exert multiple therapeutic effects (they do not act solely via a single neurotransmitter system, but often through pluripotent biological actions, such as antioxidant property, modulation of neurotransmitters (e.g. Learning and memory processes), improved cerebral blood flow, and neurotrophic action. [54,55]

Typically, herbal nootropics have complex phytochemical profiles and show a variety of bioactivities due to the presence of various active compounds including flavonoids, terpenoids, saponins and alkaloids that are responsible for cognitive enhancing effects. Many of these compounds are polar and water soluble, which can hinder in vivo bioavailability by preventing them from crossing lipid-containing biological membranes. Aware of this fact, new formulation technologies (e.g., phytosomes, which are complex of plant extracts with phospholipids) have been proposed to overcome these limitations. The use of phytosomes improves the solubility and bioavailability of these herbal ingredients, contributing to a more effective treatment because it prevents degradation of active molecules in gastrointestinal environment and allows better absorption at site of action.

Although there is now emergent evidence that medical herbal nootropics are effective, their effects tend to be reflected through long-term rather than short-term administration. Such delayed-onset efficacy should be due to how they are working in the modulation of physiological events and the enhancement of neuroprotection than an acute response for alleviation of symptoms. It is of the essence, however, to state that although these natural

products hold promise, their pharmacokinetics profiles, the standard doses and safety need further systematic investigation in clinical studies.

In summary, the herbal nootropics are a very promising class of agents for brain health with traditional roots and emerging therapeutic significance. They provide a way to model the wisdom of traditional herbal medicine and modern pharmacology, aiming to enhance cognition, attenuate oxidative damage and promote healthy aging albeit with limited penetration through the blood brain barrier and lag time in onset. The promise of these naturally occurring cognitive enhancers continues to drive investigation, as novel methodologies make them a viable clinical target. [56,57]

Advantage Over Synthetic Drugs

For cognitive enhancement and neuroprotection, herbal nootropics have several superiorities compared to synthetic drugs. In contrast to synthetics, which usually act through a single molecular mechanism, herbal nootropics such as guarana with multiple physiologically active phytochemicals that may synergistically enhance cognitive function. Such polypharmacological action gives a wide therapeutic spectrum and theoretically more comprehensive effects, reaching not only symptoms but also possible etiological factors playing a role such as oxidative stress and inflammation. Synthetic drugs, on the other hand, are predominantly developed to bind a known target with implications in lower effectiveness and higher side effects.

Herbal nootropics also have one more thing under their belt - safety. Serious side effects are often associated with synthetic drugs. For example, side effects from pharmaceutical drugs are responsible for about 8% of all U.S. hospital admissions (of which thousands die each year due to prescription or over-the-counter drugs). Very rarely, severe adverse reactions or poisoning from herbal medicines have been reported. This popular notion of their safety is the reason many people are attracted to herbal medicines as a safer option, (but it should be remembered that there can be harm if wrongly identified or misused).

In addition, herbal nootropics are generally mild and may be acting in a way to support or balance normal functions (rather than inducing action). Synthetic medications frequently are designed to address the symptoms or provide immediate treatment, even though long-term damage can result, or addictiveness may be an issue. Through multiple bioactive compounds with various mechanisms of action, herbs can be utilized to promote innate healing processes and balance physiological homeostasis such as antioxidant response, inflammation mediating pathways, and neurotrophic factor modulation. This integrated approach is less perturbing and toxic than the sometimes-unrefined action of synthetic molecules.

And then there's the accessibility and price point favoring herbal nootropics. Although there are plenty of nootropics that don't require prescription but are too expensive to buy on a regular basis, herbal nootropics can be found over the counter and have been 3139-2741 throughout history across countless cultures for medicinal purposes. This accessibility enables broader use

with a minimum of regulatory concerns, although standardization and quality control issues remain to be confronted.

But as much as herbal nootropics possess these benefits, there are some setbacks too. Pharmacokinetics Their full pharmacokinetics can be unpredictable since they often compose of mixed herbal preparation. Long-term clinical data regarding efficacy and safety, particularly in comparison to rigorously studied synthetic drugs, are also still forthcoming. However, a multi-level influence, better tolerability and their profile of action make the reason to pursue research and inclusion in cognitive enhancement therapies.

In a word, the herbal nootropics have the following advantages of multi-target action, lower risk of serious adverse reaction, support for multiple physiological functions and accessible to all compared with synthetic drugs. These compares vales look like promising, if underutilized, adjuvants or alternatives in nootropic pharmacotherapy. [58–60]

Regulatory and Standardization Issues

Herbal nootropics showing cognitive activity looks promising; however, they must address huge issues of regulation and standardization which in turn will impact the clinical acceptability and safe usage. In the contrast to the synthetic drugs, plant products are a library for multiple bioactive compounds. This framework makes regulatory appraisal and standardization work more complex. It is not easy to define purity, potency and identity, as these characteristics can be dependent on species, plant part of the source material, geographical origin, method of cultivation and extraction. So, no uniform standards. This heterogeneity is a major obstacle in the way of quality control and regulatory monitoring.

Another major problem is classification. Herbal nootropics are typically in a gray area of regulation, varying by country sometimes as dietary supplements, other times as herbal medicines, traditional medicines or not classified at all. This incoherence results in regulatory grey areas, which hampers the development of aligned policy and strengthens the implementation of safety and effectiveness criteria. For instance, while in some countries herbal products are sold without strict pre-market testing requirement, others require that many of the same tests required for pharmaceuticals be carried out. This regulation patchwork may even have products containing the same ingredients subjected to different even less stringent requirements, which can put consumers at risk from substandard or adulterated products.

Additionally, adulteration and contamination present a risk to product quality control. Herbs can be intentionally adulterated, laced with synthetic drugs or cheaper fillers that mimic the activity of a particular herb; they can also be unintentionally contaminated with heavy metals, pesticides and microbes. Stability is also a problem, as herbal formulations can become spoiled by environmental conditions such as heat, humidity and light. These require stringent monitoring, however the manpower and funding to enforce such regulations are frequently scarce in many countries.

Modern technologies such as phytochemical screening through chromatographic approaches, DNA barcoding for botanical identity and GACP (Good Agricultural Collection Practices) have been developed to combat these issues. But they are expensive and require a high level of

skill and so are not widely used, particularly in low-income areas. Equally those pharmacopeial monographs which give exact standards for individual herbs enhance control, but they are neither readily available nor standardised on a global.

The absence of uniform regulations is not conducive for herbal nootropics producers, especially small and medium enterprises that find it difficult to meet different specifications in different markets. In addition, there is no international finding of quality standard to further hinder the above products for global trade and utilization. Partnerships among regulators and policymakers, scientists, industry stakeholders & healthcare professionals are proposed as a way forward to set in place common guidelines and standards to ensure safety efficacy \& consistency in this expanding category of cognitive enhancers. In summary, the regulatory and standardization challenges for herbal nootropics are large and combinatorial. They are challenges for science to solve, resources to be allocated and international cooperation to address. Without those steps, the complete medicinal value of herbal nootropics can't be harnessed safely or properly so perhaps even for modern medication. [61–63]

Prominent Herbal Nootropics Studied in Dementia

Botanical Nootropics have been recently elevated to the mainstream of interest in studies related to dementia because of their multi-interventional pharmacodynamics and relatively safer toxic profiles than synthetic drugs. Several botanicals, particularly those from traditional Ayurvedic medicine and other natural systems, have been widely investigated for their ability to ameliorate cognitive dysfunction associated with dementia (e.g., Alzheimer's disease [AD]). [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. [66,67]

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. [68,69]

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. [73,74]

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. [75,76]

12. Botanical Name: *Curcuma longa*
Common Name: Turmeric, Curcumin
Genus and Family: Genus: Curcuma
Family: Zingiberaceae
Parts Used: The root (rhizoma) is the part utilized, either as a spice or herb.

About the Plant

Turmeric extract (*Curcuma longa*, also known as the golden spice) is a perennial herb belonging to the ginger family that originated from South Asia. For thousands of years, it has been utilized by traditional Indian and Chinese medicine to treat inflammation and promote overall health. The dried rhizomes contain a yellow-colored chemical called curcumin, which is the source of most of turmeric's health benefits. It's eaten world-wide in cooking and as a tonic, lauded for its purported ability to slow aging and enhance brain health. Curcumin is famous, but it's also naturally poorly absorbed and quickly metabolized obstacles that 21st century science must still address via novel delivery systems.

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.[77,78]

Botanical Name: *Nardostachys jatamansi*
Common Name: Spikenard
Genus and Family: Genus: Nardostachys
Family: Valerianaceae
Parts Used: Roots and rhizomes are mainly used in previous studies or Chinese traditional medicine.

About the Plant

Spikenard is a perennial herb which grows up to 70 cm in height, with very hairy stems and lower leaves. It's been used in Ayurveda and traditional medicine for centuries as a tranquilizer and neuroprotectant. Considered to be a holy herb in many cultures, it is revered as much for its lovely scent as its purported ability to increase focus and decrease stress and cognitive decline. The plant is high altitude and has a robust, bushy look with dainty pretty flowers.

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. [79–81]

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. [82,83]

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. [84]

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. [85]

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. [86]

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. [89]

Preclinical Studies of Herbal Nootropics

Animal trials are the hub of preclinical dementia research, presenting a good testing ground for herbal nootropics. The model of dementia induced by scopolamine is commonly used. Scopolamine keeps acetylcholine from attaching to synapses, effectively zapping memory and behaving like the early stages of Alzheimer's dementia. Numerous plant molecules such as polyphenols, alkaloids and terpenoids counteract scopolamine-produced memory loss and attenuate oxidative stress and brain inflammation.

Besides, Polyphenols in plants like quercetin and resveratrol mop up dangerous free radicals in the brain and fuel neuronal survival. They uplift antioxidant enzymes SOD and CAT as well aiding in balancing internal environment. Flavonoids exert their action on brain-derived neurotrophic factor (BDNF), a protein that supports both neurogenesis and synaptic plasticity. Compounds such as the alkaloid huperzine A from Huperzia serrata are acetylcholinesterase inhibitors. By slowing the body's breakdown of acetylcholine, they enhance neurotransmission that is crucial for learning and memory. Huperzine A also exhibits anti-inflammatory20–22) and anti-apoptotic23,24 effects in the brain by preventing nerve cell death.Terpenoids (eg from ginseng and turmeric) act by suppressing inflammatory pathways including NF-κB and decreasing the release of cytokines such as TNF-α and interleukins. They can enhance mitochondrial health and maintain neuronal energy. Synergistic effects are blunted when multiple herbal compounds are combined to increase protective effects against pathologies, such as cholinergic and oxidative dysfunction and protein aggregation observed in dementia models.

Several behavioral tests including Morri's water maze (MWM), Y-maze, and novel object recognition (NOR) test are employed to investigate the improvements in spatial memory, working memory, and recognition following administration of herbal extracts in these models. Taken together, preclinical evidence shows herbal nootropics have multiple pathways against dementia pathology and are, hence, potential candidates deserving further development. (90)

Overview of Studies and Meta-Analyses

Clinical trials of herbal nootropics seem to have promising findings although they are often small of short duration. One of the most commonly studied may offer mild but reliable improvement in cognitive function, daily living activities and neuropsychiatric symptoms in patients with mild-to-moderate dementia. Its safety and mild effectiveness are confirmed by a meta-analyzes, particularly if standardized extracts such as EGb 761 are considered.

Curcumin supplementation shows potential effects on prevention of brain inflammation and oxidative stress markers with some evidence for cognitive improvement. But its low bioavailability is a factor; newer formulations are in clinical development.

Combination treatments, including herbal nootropics with approved drugs for dementia commonly demonstrate additive cognitive benefits and decreased side effects. Therefore, meta-analyses are consistent in finding that herbal nootropics have potential to be used as adjuvant therapy, but more large-scale, high-quality RCTs with standardized measurements are needed for definitive answers.

In one word, pre-clinical and clinical evidence indicates that herbal nootropics effectively act on several dementia pathways and may alleviate symptoms of dementia, thereby serving a complementary purpose with negligible side-effects. Future studies will determine the best combinations, doses and long-term effects in controlling dementia. [91,92]

14. Challenges in Translating Animal Data to Clinical Practice

Animal studies are important in dementia work we have no doubt about that. The brains of animals, particularly rodents, are not like our brains. Most animal models use shortcuts, such

as toxins or genetic tweaks, to develop symptoms quickly. But in people, dementia comes slowly over decades and results from a complex interplay of factors like aging, environment and genes. Animals are knocked out quickly and gutted, so it's hard to know what will work in them that will solve the slow, complicated human disorder.

Dosing is a big headache too. And what is safe and effective in mice may not be the same for humans. They have different potentials for metabolism, and the side effects can be completely unpredictable. And then there's the fact that a lot of these studies have issues, such as small numbers of animals, inadequate controls or bias, so the findings may not be sound.

Even shiny new transgenic models featuring human genes associated with Alzheimer's or other dementias don't paint the full human picture. They can get plaques or tangles. On some occasions, the brain degeneration is mild or absent, which is less amenable to testing drugs that could make a real difference.

And emulating the yearslong period of silence during dementia in a short animal study is nearly impossible. There is no such thing as the perfect animal model, only us imperfect tools that we are trying to use one way and another. That's what people should be doing now is taking some of these animal studies and marrying them to human cell study, computer models and better trial designs. It's slow, frustrating work, but we need to keep trying. For without animal data, we wouldn't even be looking in the correct direction. [93,94]

15. Future Directions and Challenges

A. Need for Standardized Extracts and Dosing

Lack of standardization is a huge headache with herbal medicines. Extracts made from the same plant can contain wildly varying chemical cocktails, thanks largely to variations in growing conditions, when a plant was harvested and how it's been processed, even stored. We need sound guidance on extract quality and dose, badly. Otherwise, patients and doctors are operating in the dark and research findings become difficult to replicate or trust. [95]

B. Lack of Large-scale Multicenter Clinical Trials

Most of the clinical studies on herbal nootropics are small, short-term and single center based. That's simply not enough for a complex disease as slow-moving and variable in its presentation among people as dementia. We need large, multicenter, longer-term studies in a diverse population. That will help pick up real-world effectiveness and safety. Without them, promising treatments have difficulty being accepted and regulatory approval seems remote. Improved financing and greater international cooperation are essential to close these gaps. [96,97]

C. Interactions of Herbs and Drugs/Safety Monitoring

There's a clear need for research, researchers said, particularly in dementia, where polypharmacy is common; many people take herbal remedies at home along with prescription medicine. But we understand staggeringly little about how these herbs interact with conventional medications. Given that plant compounds can influence drug-metabolizing enzymes and/or neurotransmitter systems, they have the potential to generate adverse side effects or diminish the effectiveness of clinical drugs. To safety-monitor herb-drug

interactions is widely ignored. To prevent surprises and to facilitate safe use, there is need for reliable reporting systems, patient education and organized care. [98,99]

D. Integrate Approaches and Combination Therapies

Dementia is a multifaceted beast. No drug alone nails all the right targets. With their multicomponent nature, herbal medications may serve as adjuvants of standard drugs by targeting various pathways for neuroprotection, inflammation, oxidative stress and neurotransmitter support. Mixing herbs and drugs may magnify benefits and cut down on side effects. But indiscriminately combining treatments without thoughtful design can do harm and perhaps even dilute effectiveness. Integrative methods need to be accurately formulated, thoroughly tried and tested, based on individualized medicine principles and monitored closely in the clinical environment. This is a fascinating yet demanding frontier that requires inter-discipline cooperation. [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

REFERENCES

1. Abdul Manap, A. S., Vijayabalan, S., Madhavan, P., Chia, Y. Y., Arya, A., Wong, E. H., Rizwan, F., Bindal, U., & Koshy, S. (2019). *Bacopa monnieri*, a neuroprotective lead in Alzheimer disease: A review on its properties, mechanisms of action, and preclinical and clinical studies. *Drug Target Insights, 13*(1), 1177392819866412. https://doi.org/10.1177/1177392819866412

2. Adolphs, R., Sears, L., & Piven, J. (2001). Abnormal processing of social information from faces in autism. *Journal of Cognitive Neuroscience, 13*(2), 232–240. https://doi.org/10.1162/089892901564289

3. Agarwal, P., Sharma, B., Fatima, A., & Jain, S. K. (2014). An update on Ayurvedic herb *Convolvulus pluricaulis* Choisy. *Asian Pacific Journal of Tropical Biomedicine, 4*(3), 245–252. https://doi.org/10.1016/S2221-1691(14)60240-9

4. Akhondzadeh, S., Noroozian, M., Mohammadi, M., Ohadinia, S., Jamshidi, A. H., & Khani, M. (2003). *Salvia officinalis* extract in the treatment of patients with mild to moderate Alzheimer's disease: A double-blind, randomized and placebo-controlled trial. *Journal of Clinical Pharmacy and Therapeutics, 28*(1), 53–59. https://doi.org/10.1046/j.1365-2710.2003.00463.x

5. Al Akeel, M. M., Al Ghamdi, W. M., Al Habib, S., Koshm, M., & Al Otaibi, F. (2018). Herbal medicines: Saudi population knowledge, attitude, and practice at a glance. *Journal of Family Medicine and Primary Care, 7*(5), 865–875. https://doi.org/10.4103/jfmpc.jfmpc_315_17

6. Al-Karawi, D., Al Mamoori, D. A., & Tayyar, Y. (2016). The role of curcumin administration in patients with major depressive disorder: Mini meta-analysis of clinical trials. *Phytotherapy Research, 30*(2), 175–183. https://doi.org/10.1002/ptr.5524

7. Albers, M. W., Gilmore, G. C., Kaye, J., Murphy, C., Wingfield, A., Bennett, D. A., Boxer, A. L., Buchman, A. S., Cruickshanks, K. J., Devanand, D. P., et al. (2015). At the interface of sensory and motor dysfunctions and Alzheimer's disease. *Alzheimer's & Dementia, 11*(1), 70–98. https://doi.org/10.1016/j.jalz.2014.04.514

8. Alford, C., Cox, H., & Wescott, R. (2001). The effects of Red Bull energy drink on human performance and mood. *Amino Acids, 21*(2), 139–150. https://doi.org/10.1007/s007260170021

9. Asadi, S., Gholami, M. S., Siassi, F., Qorbani, M., & Sotoudeh, G. (2020). Beneficial effects of nano-curcumin supplement on depression and anxiety in diabetic patients with peripheral neuropathy: A randomized, double-blind, placebo-controlled clinical trial. *Phytotherapy Research, 34*(4), 896–903. https://doi.org/10.1002/ptr.6571

10. Attia, A., Rapp, S. R., Case, L. D., D'Agostino, R., Lesser, G., Naughton, K., McMullen, K., Rosdhal, R., & Shaw, E. G. (2012). Phase II study of *Ginkgo biloba* in irradiated brain tumor patients: Effect on cognitive function, quality of life, and mood. *Journal of Neuro-Oncology, 109*(2), 357–363. https://doi.org/10.1007/s11060-012-0901-9

11. Bakhtiari, M., Panahi, Y., Ameli, J., & Darvishi, B. (2017). Protective effects of flavonoids against Alzheimer's disease-related neural dysfunctions. *Biomedicine & Pharmacotherapy, 93*, 218–229. https://doi.org/10.1016/j.biopha.2017.06.010
12. Ball, G., Stokes, P. R., Rhodes, R. A., Bose, S. K., Rezek, I., Wink, A. M., Lord, L. D., Mehta, M. A., Grasby, P. M., & Turkheimer, F. E. (2011). Executive functions and prefrontal cortex: A matter of persistence? *Frontiers in Systems Neuroscience, 5*, 3. https://doi.org/10.3389/fnsys.2011.00003
13. Banerjee, S., Anand, U., Ghosh, S., Ray, D., Ray, P., Nandy, S., Deshmukh, G. D., Tripathi, V., & Dey, A. (2021). Bacosides from *Bacopa monnieri* extract: An overview of the effects on neurological disorders. *Phytotherapy Research, 35*(10), 5668–5679. https://doi.org/10.1002/ptr.7203
14. Barbhaiya, H. C., Desai, R. P., Saxena, V. S., Pravina, K., Wasim, P., Geetharani, P., Allan, J. J., Venkateshw, K., & Amit, A. (2008). Efficacy and tolerability of BacoMind® on memory improvement in elderly participants: A double-blind placebo-controlled study. *Journal of Pharmacology and Toxicology, 3*(6), 425–434. https://doi.org/10.3923/jpt.2008.425.434
15. Barry, R. J., Johnstone, S. J., Clarke, A. R., Rushby, J. A., Brown, C. R., & McKenzie, D. N. (2007). Caffeine effects on ERPs and performance in an auditory Go/NoGo task. *Clinical Neurophysiology, 118*(12), 2692–2699. https://doi.org/10.1016/j.clinph.2007.08.023
16. Le Bars, P. (2003). Response patterns of EGb 761® in Alzheimer's disease: Influence of neuropsychological profiles. *Pharmacopsychiatry, 36*(Suppl 1), S50–S55. https://doi.org/10.1055/s-2003-40456
17. Bäurle, P., Suter, A., & Wormstall, H. (2009). Safety and effectiveness of a traditional ginkgo fresh plant extract: Results from a clinical trial. *Forschende Komplementärmedizin, 16*(3), 156–161. https://doi.org/10.1159/000213167
18. Belcaro, G., Dugall, M., Ippolito, E., Hu, S., Saggino, A., & Feragalli, B. (2015). The COFU3 study: Improvement in cognitive function, attention, and mental performance with Pycnogenol® in healthy subjects (55–70) with high oxidative stress. *Journal of Neurosurgical Sciences, 59*(4), 437–446.
19. Bell, L., Lamport, D. J., Butler, L. T., & Williams, C. M. (2015). A review of the cognitive effects observed in humans following acute supplementation with flavonoids and their associated mechanisms of action. *Nutrients, 7*(12), 10290–10306. https://doi.org/10.3390/nu7125538
20. Bell, L., Whyte, A. R., Lamport, D. J., Spencer, J. P. E., Butler, L. T., & Williams, C. M. (2020). Grape seed polyphenol extract and cognitive function in healthy young adults: A randomized, placebo-controlled, parallel-groups acute-on-chronic trial. *Nutritional Neuroscience.* https://doi.org/10.1080/1028415X.2019.1708033
21. Bell, L., & Williams, C. M. (2019). A pilot dose-response study of the acute effects of haskap berry extract (*Lonicera caerulea* L.) on cognition, mood, and blood pressure in older adults. *European Journal of Nutrition, 58*(8), 3325–3334. https://doi.org/10.1007/s00394-018-1877-9

22. Benson, S., Downey, L. A., Stough, C., Wetherell, M., Zangara, A., & Scholey, A. (2014). An acute, double-blind, placebo-controlled cross-over study of 320 mg and 640 mg doses of *Bacopa monnieri* (CDRI 08) on multitasking stress reactivity and mood. *Phytotherapy Research, 28*(4), 551–559. https://doi.org/10.1002/ptr.5029
23. Benson, S., Tiplady, B., & Scholey, A. (2019). Attentional and working memory performance following alcohol and energy drink: A randomized, double-blind, placebo-controlled factorial design laboratory study. *PLoS ONE, 14*(1), e0209239. https://doi.org/10.1371/journal.pone.0209239
24. Blair, C. (2016). Developmental science and executive function. *Current Directions in Psychological Science, 25*(1), 3–7. https://doi.org/10.1177/0963721415622634
25. Brimson, J. M., Brimson, S., Prasanth, M. I., Thitilertdecha, P., Malar, D. S., & Tencomnao, T. (2021). The effectiveness of *Bacopa monnieri* (Linn.) Wettst. as a nootropic, neuroprotective, or antidepressant supplement: Analysis of the available clinical data. *Scientific Reports, 11*(1), 596. https://doi.org/10.1038/s41598-020-80045-2
26. Burns, N. R., Bryan, J., & Nettelbeck, T. (2006). *Ginkgo biloba*: No robust effect on cognitive abilities or mood in healthy young or older adults. *Human Psychopharmacology: Clinical and Experimental, 21*(1), 27–37. https://doi.org/10.1002/hup.739
27. Calabrese, C., Gregory, W. L., Leo, M., Kraemer, D., Bone, K., & Oken, B. (2008). Effects of a standardized *Bacopa monnieri* extract on cognitive performance, anxiety, and depression in the elderly: A randomized, double-blind, placebo-controlled trial. *Journal of Alternative and Complementary Medicine, 14*(6), 707–713. https://doi.org/10.1089/acm.2008.0018
28. Camfield, D. A., Scholey, A. B., Pipingas, A., Silberstein, R. B., Kure, C., Zangara, A., Kras, M., & Stough, C. (2013). The neurocognitive effects of *Hypericum perforatum* special extract (Ze 117) during smoking cessation. *Phytotherapy Research, 27*(11), 1605–1613. https://doi.org/10.1002/ptr.4909
29. Camfield, D. A., Stough, C., Farrimond, J., & Scholey, A. B. (2014). Acute effects of tea constituents L-theanine, caffeine, and epigallocatechin gallate on cognitive function and mood: A systematic review and meta-analysis. *Nutrition Reviews, 72*(8), 507–522. https://doi.org/10.1111/nure.12120
30. Canter, P. H., & Ernst, E. (2003). Multiple n = 1 trials in the identification of responders and non-responders to the cognitive effects of *Ginkgo biloba*. *International Journal of Clinical Pharmacology and Therapeutics, 41*(8), 354–357. https://doi.org/10.5414/cpp41354
31. Canter, P. H., & Ernst, E. (2007). *Ginkgo biloba* is not a smart drug: An updated systematic review of randomized clinical trials testing the nootropic effects of *Ginkgo biloba* extracts in healthy people. *Human Psychopharmacology: Clinical and Experimental, 22*(5), 265–278. https://doi.org/10.1002/hup.843
32. Cappelletti, S., Piacentino, D., Daria, P., Sani, G., & Aromatario, M. (2015). Caffeine: Cognitive and physical performance enhancer or psychoactive drug? *Current Neuropharmacology, 13*(1), 71–88. https://doi.org/10.2174/1570159X13666141210215655

33. Carrillo, J. A., & Benitez, J. (2000). Clinically significant pharmacokinetic interactions between dietary caffeine and medications. *Clinical Pharmacokinetics, 39*(2), 127–153. https://doi.org/10.2165/00003088-200039020-00004
34. Chan, P. C., Xia, Q., & Fu, P. P. (2007). *Ginkgo biloba* leaf extract: Biological, medicinal, and toxicological effects. *Journal of Environmental Science and Health, Part C, Environmental Carcinogenesis and Ecotoxicology Reviews, 25*(3), 211–244. https://doi.org/10.1080/10590500701569414
35. Chandrasekhar, K., Kapoor, J., & Anishetty, S. (2012). A prospective, randomized double-blind, placebo-controlled study of safety and efficacy of a high-concentration full-spectrum extract of ashwagandha root in reducing stress and anxiety in adults. *Indian Journal of Psychological Medicine, 34*(3), 255–262. https://doi.org/10.4103/0253-7176.106022
36. Chengappa, K. N. R., Bowie, C. R., Schlicht, P. J., Fleet, D., Brar, J. S., & Jindal, R. (2013). Randomized placebo-controlled adjunctive study of an extract of *Withania somnifera* for cognitive dysfunction in bipolar disorder. *Journal of Clinical Psychiatry, 74*(11), 1076–1083. https://doi.org/10.4088/JCP.13m08413
37. Choudhary, D., Bhattacharyya, S., & Bose, S. (2017). Efficacy and safety of ashwagandha (*Withania somnifera* [L.] Dunal) root extract in improving memory and cognitive functions. *Journal of Dietary Supplements, 14*(6), 599–612. https://doi.org/10.1080/19390211.2017.1284970
38. Choudhary, D., Bhattacharyya, S., & Joshi, K. (2017). Body weight management in adults under chronic stress through treatment with ashwagandha root extract: A double-blind, randomized, placebo-controlled trial. *Journal of Evidence-Based Complementary & Alternative Medicine, 22*(1), 96–106. https://doi.org/10.1177/2156587216641830
39. Christopher, G., Sutherland, D., & Smith, A. (2005). Effects of caffeine in non-withdrawn volunteers. *Human Psychopharmacology: Clinical and Experimental, 20*(1), 47–53. https://doi.org/10.1002/hup.658
40. Crews, W. D., Harrison, D. W., Griffin, M. L., Addison, K., Yount, A. M., Giovenco, M. A., & Hazell, J. (2005). A double-blinded, placebo-controlled, randomized trial of the neuropsychologic efficacy of cranberry juice in cognitively intact older adults: Pilot study findings. *Journal of Alternative and Complementary Medicine, 11*(2), 305–309. https://doi.org/10.1089/acm.2005.11.305
41. Dai, C. X., Hu, C. C., Shang, Y. S., & Xie, J. (2018). Role of *Ginkgo biloba* extract as an adjunctive treatment of elderly patients with depression and on the expression of serum S100B. *Medicine, 97*(39), e12421. https://doi.org/10.1097/MD.0000000000012421
42. Daily, J. W., Yang, M., & Park, S. (2016). Efficacy of turmeric extracts and curcumin for alleviating the symptoms of joint arthritis: A systematic review and meta-analysis of randomized clinical trials. *Journal of Medicinal Food, 19*(8), 717–729. https://doi.org/10.1089/jmf.2016.3705

43. Daly, J. W., Holmén, J., & Fredholm, B. B. (1998). Is caffeine addictive? The most widely used psychoactive substance in the world affects the same parts of the brain as cocaine. *Lakartidningen, 95*(51–52), 5878–5883.
44. Davidson, M. G. (2011). Herbal-caffeinated chewing gum, but not bubble gum, improves aspects of memory. *Appetite, 57*(1), 303–307. https://doi.org/10.1016/j.appet.2011.04.019
45. De Pauw, K., Roelands, B., Knaepen, K., Polfliet, M., Stiens, J., & Meeusen, R. (2015). Effects of caffeine and maltodextrin mouth rinsing on P300, brain imaging, and cognitive performance. *Journal of 3139-2741 Physiology, 118*(6), 776–782. https://doi.org/10.1152/japplphysiol.01050.2014
46. Decroix, L., Soares, D. D., Meeusen, R., Heyman, E., & Tonoli, C. (2018). Cocoa flavanol supplementation and exercise: A systematic review. *Sports Medicine, 48*(4), 867–892. https://doi.org/10.1007/s40279-017-0849-1
47. Diamond, B. J., Shiflett, S. C., Feiwel, N., Matheis, R. J., Noskin, O., Richards, J. A., & Schoenberger, N. E. (2000). *Ginkgo biloba* extract: Mechanisms and clinical indications. *Archives of Physical Medicine and Rehabilitation, 81*(5), 668–678. https://doi.org/10.1016/S0003-9993(00)90052-2
48. Diamond, B. J., Johnson, S. K., Kaufman, M., Shiflett, S. C., & Graves, L. (2013). A randomized controlled pilot trial: The effects of EGb 761 on information processing and executive function in multiple sclerosis. *Explore, 9*(2), 106–107. https://doi.org/10.1016/j.explore.2012.12.001
49. Dietz, C., Dekker, M., & Piqueras-Fiszman, B. (2017). An intervention study on the effect of matcha tea, in drink and snack bar formats, on mood and cognitive performance. *Food Research International, 99*(Pt 1), 72–83. https://doi.org/10.1016/j.foodres.2017.05.002
50. Dimpfel, W., Schombert, L., Keplinger-Dimpfel, I. K., & Panossian, A. (2020). Effects of an adaptogenic extract on electrical activity of the brain in elderly subjects with mild cognitive impairment: A randomized, double-blind, placebo-controlled, two-armed cross-over study. *Pharmaceuticals, 13*(3), 45. https://doi.org/10.3390/ph13030045
51. Dodge, H. H., Zitzelberger, T., Oken, B. S., Howieson, D., & Kaye, J. (2008). A randomized placebo-controlled trial of *Ginkgo biloba* for the prevention of cognitive decline. *Neurology, 70*(19 Pt 2), 1809–1817. https://doi.org/10.1212/01.wnl.0000303814.13509.db
52. Downey, L. A., Kean, J., Nemeh, F., Lau, A., Poll, A., Gregory, R., Murray, M., Rourke, J., Patak, B., Pase, M. P., et al. (2013). An acute, double-blind, placebo-controlled crossover study of 320 mg and 640 mg doses of a special extract of *Bacopa monnieri* (CDRI 08) on sustained cognitive performance. *Phytotherapy Research, 27*(9), 1407–1413. https://doi.org/10.1002/ptr.4864
53. Dubey, T., & Chinnathambi, S. (2019). Brahmi (*Bacopa monnieri*): An Ayurvedic herb against Alzheimer's disease. *Archives of Biochemistry and Biophysics, 676*, 108153. https://doi.org/10.1016/j.abb.2019.108153
54. Dutta, B., Park, J. E., Kumar, S., Hao, P., Gallart-Palau, X., Serra, A., Ren, Y., Sorokin, V., Lee, C. N., Ho, H. H., et al. (2017). Monocyte adhesion to atherosclerotic matrix proteins

is enhanced by Asn-Gly-Arg deamidation. *Scientific Reports, 7*(1), 5765. https://doi.org/10.1038/s41598-017-06202-2

55. Ellis, K. A., Stough, C., Vitetta, L., Heinrich, K., & Nathan, P. J. (2001). An investigation into the acute nootropic effects of *Hypericum perforatum* L. (St. John's Wort) in healthy human volunteers. *Behavioural Pharmacology, 12*(3), 173–182. https://doi.org/10.1097/00008877-200105000-00003

56. Elsabagh, S., Hartley, D. E., Ali, O., Williamson, E. M., & File, S. E. (2005). Differential cognitive effects of *Ginkgo biloba* after acute and chronic treatment in healthy young volunteers. *Psychopharmacology, 179*(2), 437–446. https://doi.org/10.1007/s00213-005-2206-6

57. Elsabagh, S., Hartley, D. E., & File, S. E. (2005). Limited cognitive benefits in stage +2 postmenopausal women after 6 weeks of treatment with *Ginkgo biloba*. *Journal of Psychopharmacology, 19*(2), 173–181. https://doi.org/10.1177/0269881105049038

58. Esmaily, H., Sahebkar, A., Iranshahi, M., Ganjali, S., Mohammadi, A., Ferns, G., & Ghayour-Mobarhan, M. (2015). An investigation of the effects of curcumin on anxiety and depression in obese individuals: A randomized controlled trial. *Chinese Journal of Integrative Medicine, 21*(5), 332–338. https://doi.org/10.1007/s11655-015-2160-z

59. Evans, H. M., Howe, P. R., & Wong, R. H. (2017). Effects of resveratrol on cognitive performance, mood, and cerebrovascular function in postmenopausal women: A 14-week randomized placebo-controlled intervention trial. *Nutrients, 9*(1), 27. https://doi.org/10.3390/nu9010027

60. Evans, V. (2012). Cognitive linguistics. *Wiley Interdisciplinary Reviews: Cognitive Science, 3*(2), 129–141. https://doi.org/10.1002/wcs.1163

61. Farooqui, A. A., Farooqui, T., Madan, A., Ong, J. H. J., & Ong, W. Y. (2018). Ayurvedic medicine for the treatment of dementia: Mechanistic aspects. *Evidence-Based Complementary and Alternative Medicine, 2018*, 2481076. https://doi.org/10.1155/2018/2481076

62. Ferré, S. (2008). An update on the mechanisms of the psychostimulant effects of caffeine. *Journal of Neurochemistry, 105*(4), 1067–1079. https://doi.org/10.1111/j.1471-4159.2007.05196.x

63. Franceschini, S., Lulli, M., Bertoni, S., Gori, S., Angrilli, A., Mancarella, G., Puccio, G., & Facoetti, A. (2020). Caffeine improves text reading and global perception. *Journal of Psychopharmacology, 34*(3), 315–325. https://doi.org/10.1177/0269881119878178

64. Frith, U., & Blakemore, S. J. (2006). Social cognition. In *Cognitive systems: Information processing meets brain science* (pp. 138–162). Academic Press.

65. Froestl, W., Muhs, A., & Pfeifer, A. (2012). Cognitive enhancers (nootropics). Part 1: Drugs interacting with receptors. *Journal of Alzheimer's Disease, 32*(4), 793–887. https://doi.org/10.3233/JAD-2012-121186

66. Fusar-Poli, L., Vozza, L., Gabbiadini, A., Vanella, A., Concas, I., Tinacci, S., Petralia, A., Signorelli, M. S., & Aguglia, E. (2020). Curcumin for depression: A meta-analysis. *Critical*

Reviews in Food Science and Nutrition, 60(15), 2643–2653. https://doi.org/10.1080/10408398.2019.1653260

67. Gallart-Palau, X., Guo, X., Serra, A., & Sze, S. K. (2020). Alzheimer's disease progression characterized by alterations in the molecular profiles and biogenesis of brain extracellular vesicles. *Alzheimer's Research & Therapy, 12*(1), 54. https://doi.org/10.1186/s13195-020-00623-4

68. Gallart-Palau, X., Serra, A., Hase, Y., Tan, C. F., Chen, C. P., Kalaria, R. N., & Sze, S. K. (2019). Brain-derived and circulating vesicle profiles indicate neurovascular unit dysfunction in early Alzheimer's disease. *Brain Pathology, 29*(5), 593–605. https://doi.org/10.1111/bpa.12699

69. Gallart-Palau, X., Tan, L. M., Serra, A., Gao, Y., Ho, H. H., Richards, A. M., Kandiah, N., Chen, C. P., Kalaria, R. N., & Sze, S. K. (2019). Degenerative protein modifications in the aging vasculature and central nervous system: A problem shared is not always halved. *Ageing Research Reviews, 53*, 100909. https://doi.org/10.1016/j.arr.2019.100909

70. Gallart-Palau, X., Tarabal, O., Casanovas, A., Sábado, J., Correa, F. J., Hereu, M., Piedrafita, L., Calderó, J., & Esquerda, J. E. (2014). Neuregulin-1 is concentrated in the postsynaptic subsurface cistern of C-bouton inputs to α-motoneurons and altered during motoneuron diseases. *FASEB Journal, 28*(8), 3618–3632. https://doi.org/10.1096/fj.13-248583

71. Gallart-Palau, X., Serra, A., & Sze, S. K. (2020). System-wide molecular dynamics of endothelial dysfunction in Gram-negative sepsis. *BMC Biology, 18*(1), 175. https://doi.org/10.1186/s12915-020-00914-0

72. Gannon, J. M., Brar, J., Rai, A., & Chengappa, K. N. R. (2019). Effects of a standardized extract of *Withania somnifera* (ashwagandha) on depression and anxiety symptoms in persons with schizophrenia participating in a randomized, placebo-controlled clinical trial. *Annals of Clinical Psychiatry, 31*(2), 123–129.

73. Gao, X., Cassidy, A., Schwarzschild, M. A., Rimm, E. B., & Ascherio, A. (2012). Habitual intake of dietary flavonoids and risk of Parkinson disease. *Neurology, 78*(15), 1138–1145. https://doi.org/10.1212/WNL.0b013e31824f7fc4

74. Gavrilova, S. I., Preuss, U. W., Wong, J. W., Hoerr, R., Kaschel, R., Bachinskaya, N., & GIMCIPlus Study Group. (2014). Efficacy and safety of *Ginkgo biloba* extract EGb 761 in mild cognitive impairment with neuropsychiatric symptoms: A randomized, placebo-controlled, double-blind, multicenter trial. *International Journal of Geriatric Psychiatry, 29*(10), 1087–1095. https://doi.org/10.1002/gps.4103

75. Goel, B., & Maurya, N. (2019). Memory booster herb (natural cognitive enhancers): An overview. *International Journal of Physiology, Nutrition and Physical Education, 4*(1), 975–979.

76. Goutman, S. A. (2017). Diagnosis and clinical management of amyotrophic lateral sclerosis and other motor neuron disorders. *Continuum: Lifelong Learning in Neurology, 23*, 1332–1359. https://doi.org/10.1212/CON.0000000000000535

77. Gschwind, Y. J., Bridenbaugh, S. A., Reinhard, S., Granacher, U., Monsch, A. U., & Kressig, R. W. (2017). *Ginkgo biloba* special extract LI 1370 improves dual-task walking in patients with MCI: A randomized, double-blind, placebo-controlled exploratory study. *Aging Clinical and Experimental Research, 29*(4), 609–619. https://doi.org/10.1007/s40520-016-0699-y
78. Hartley, D. E., Elsabagh, S., & File, S. E. (2004). Gincosan (a combination of *Ginkgo biloba* and *Panax ginseng*): The effects on mood and cognition of 6 and 12 weeks' treatment in postmenopausal women. *Nutritional Neuroscience, 7*(5–6), 325–333. https://doi.org/10.1080/10284150400015557
79. Hartley, D. E., Heinze, L., Elsabagh, S., & File, S. E. (2003). Effects on cognition and mood in postmenopausal women of 1-week treatment with *Ginkgo biloba*. *Pharmacology Biochemistry and Behavior, 75*(3), 711–720. https://doi.org/10.1016/S0091-3057(03)00123-0
80. Haskell, C. F., Kennedy, D. O., Milne, A. L., Wesnes, K. A., & Scholey, A. B. (2008). The effects of L-theanine, caffeine and their combination on cognition and mood. *Biological Psychology, 77*(2), 113–122. https://doi.org/10.1016/j.biopsycho.2007.09.008
81. Haskell, C. F., Kennedy, D. O., Wesnes, K. A., Milne, A. L., & Scholey, A. B. (2007). A double-blind, placebo-controlled, multi-dose evaluation of the acute behavioural effects of guaraná in humans. *Journal of Psychopharmacology, 21*(1), 65–70. https://doi.org/10.1177/0269881106063815
82. Haskell-Ramsay, C. F., Stuart, R. C., Okello, E. J., & Watson, A. W. (2017). Cognitive and mood improvements following acute supplementation with purple grape juice in healthy young adults. *European Journal of Nutrition, 56*(8), 2621–2631. https://doi.org/10.1007/s00394-017-1454-7
83. Hill, J., Pilkonis, P., Morse, J., Feske, U., Reynolds, S., Hope, H., Charest, C., & Broyden, N. (2008). Social domain dysfunction and disorganization in borderline personality disorder. *Psychological Medicine, 38*(1), 135–146. https://doi.org/10.1017/S0033291707001626
84. Hilton, M. P., Zimmermann, E. F., & Hunt, W. T. (2013). *Ginkgo biloba* for tinnitus. *Cochrane Database of Systematic Reviews, 2013*(3), CD003852. https://doi.org/10.1002/14651858.CD003852.pub3
85. Hobbs, C., & Gardner, L. (2013). *Grow it, heal it: Natural and effective herbal remedies from your garden or windowsill*. Rodale Books.
86. Horning, S., & Davis, H. P. (2012). Aging and cognition. In *Encyclopedia of human behavior* (2nd ed., pp. 44–52). Academic Press.
87. Jauhari, N., Singh, Y. D., Kushwaha, K. P., Rastogi, C. K., Asthana, O. P., Srivastava, J. S., & Rathi, A. K. (2001). Clinical evaluation of *Bacopa monnieri* extract on behavioural and cognitive functions in children suffering from attention deficit hyperactivity disorder. Central Drug Research Institute.
88. Jeyasri, R., Muthuramalingam, P., Suba, V., Ramesh, M., & Chen, J.-T. (2020). *Bacopa monnieri* and its bioactive compounds inferred multi-target treatment strategy for neurological

diseases: A cheminformatics and system pharmacology approach. *Biomolecules, 10*(4), 536. https://doi.org/10.3390/biom10040536

89. Johnson, S. K., Diamond, B. J., Rausch, S., Kaufman, M., Shiflett, S. C., & Graves, L. (2006). The effect of *Ginkgo biloba* on functional measures in multiple sclerosis: A pilot randomized controlled trial. *Explore, 2*(1), 19–24. https://doi.org/10.1016/j.explore.2005.10.007

90. Kahathuduwa, C. N., Dhanasekara, C. S., Chin, S. H., Davis, T., Weerasinghe, V. S., Dassanayake, T. L., & Binks, M. (2018). L-theanine and caffeine improve target-specific attention to visual stimuli by decreasing mind wandering: A human functional magnetic resonance imaging study. *Nutrition Research, 49*, 67–78. https://doi.org/10.1016/j.nutres.2017.11.002

91. Kalia, L. V., & Lang, A. E. (2015). Parkinson's disease. *The Lancet, 386*(9996), 896–912. https://doi.org/10.1016/S0140-6736(14)61393-3

92. Kamimori, G. H., McLellan, T. M., Tate, C. M., Voss, D. M., Niro, P., & Lieberman, H. R. (2015). Caffeine improves reaction time, vigilance, and logical reasoning during extended periods with restricted opportunities for sleep. *Psychopharmacology, 232*(12), 2031–2042. https://doi.org/10.1007/s00213-014-3834-5

93. Kanchanatawan, B., Tangwongchai, S., Sughondhabhirom, A., Suppapitiporn, S., Hemrunrojn, S., Carvalho, A. F., & Maes, M. (2018). Add-on treatment with curcumin has antidepressive effects in Thai patients with major depression: Results of a randomized double-blind placebo-controlled study. *Neurotoxicity Research, 33*(3), 621–633. https://doi.org/10.1007/s12640-017-9860-4

94. Kaschel, R. (2009). *Ginkgo biloba*: Specificity of neuropsychological improvement—A selective review in search of differential effects. *Human Psychopharmacology, 24*(5), 345–370. https://doi.org/10.1002/hup.1037

95. Kean, J. D., Downey, L. A., & Stough, C. (2016). A systematic review of the Ayurvedic medicinal herb *Bacopa monnieri* in child and adolescent populations. *Complementary Therapies in Medicine, 29*, 56–62. https://doi.org/10.1016/j.ctim.2016.09.002

96. Kelly, S. P., Gomez-Ramirez, M., Montesi, J. L., & Foxe, J. J. (2008). L-theanine and caffeine in combination affect human cognition as evidenced by oscillatory alpha-band activity and attention task performance. *Journal of Nutrition, 138*(8), 1572S–1577S. https://doi.org/10.1093/jn/138.8.1572S

97. Kennedy, D. O., Dodd, F. L., Robertson, B. C., Okello, E. J., Reay, J. L., Scholey, A. B., & Haskell, C. F. (2011). Monoterpenoid extract of sage (*Salvia lavandulaefolia*) with cholinesterase inhibiting properties improves cognitive performance and mood in healthy adults. *Journal of Psychopharmacology, 25*(8), 1088–1100. https://doi.org/10.1177/0269881110385594

98. Kennedy, D. O., Haskell, C. F., Mauri, P. L., & Scholey, A. B. (2007). Acute cognitive effects of standardized *Ginkgo biloba* extract complexed with phosphatidylserine. *Human Psychopharmacology, 22*(4), 199–210. https://doi.org/10.1002/hup.837

99. Kennedy, D. O., Haskell, C. F., Wesnes, K. A., & Scholey, A. B. (2004). Improved cognitive performance in human volunteers following administration of guaraná (*Paullinia cupana*) extract: Comparison and interaction with *Panax ginseng*. *Pharmacology Biochemistry and Behavior, 79*(3), 401–411. https://doi.org/10.1016/j.pbb.2004.07.014
100. Kennedy, D. O., Jackson, P. A., Haskell, C. F., & Scholey, A. B. (2007). Modulation of cognitive performance following single doses of 120 mg *Ginkgo biloba* extract administered to healthy young volunteers. *Human Psychopharmacology, 22*(8), 559–566. https://doi.org/10.1002/hup.885
101. Le Bars, P. L., Velasco, F. M., Ferguson, J. M., Dessain, E. C., Kieser, M., & Hoerr, R. (2002). Influence of the severity of cognitive impairment on the effect of *Ginkgo biloba* extract EGb 761 in Alzheimer's disease. *Neuropsychobiology, 45*(1), 19–26. https://doi.org/10.1159/000048668