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Bioactive compounds and traditional herbal medicine in the treatment of dementia

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ABSTRACT

Modern pharmacological treatments for dementia, a progressive neurological disease that has a substantial worldwide burden, only slightly alleviate symptoms. Rich in bioactive substances such as polyphenols, alkaloids, terpenoids, and saponins, traditional herbal remedies have demonstrated encouraging neuroprotective benefits. Compounds with antioxidant, anti-inflammatory, anti-amyloidogenic, and cholinergic-enhancing qualities include curcumin (from *Curcuma longa*), epigallocatechin-3-gallate (EGCG) from green tea, huperzine A (from *Huperzia serrata*), and ginsenosides (from *Panax ginseng*). Clinical research has shown improvements in neuropsychiatric symptoms and cognition in people with mild-to-moderate dementia, including studies using Ginkgo biloba extract EGb 761 (240 mg/day). Furthermore, recent studies have demonstrated reduced tau and amyloid deposition with bioavailable formulations such as Theracurmin. Therapeutic potential is enhanced by developments in nanotechnology and phytopharmaceutical delivery technologies, despite pharmacokinetic challenges. Synergistic advantages may result from integrative treatments that combine conventional and herbal therapies. These plant-based therapies show potential as supplements in the comprehensive treatment of dementia, with strict standardization and clinical confirmation.

KEY WORDS

Bioactive compounds; Traditional herbal medicine; Dementia; Neuroprotection; Cognitive decline

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Introduction

A set of long-term, progressive neurodegenerative diseases known as dementia is characterized by a fall in memory, executive function, language, and behavior, which eventually interferes with day-to-day activities. According to estimates from the World Health Organization (WHO), over 10 million new cases of dementia are diagnosed each year, and over 55 million individuals worldwide suffer from the disease. About 60–70% of dementia cases are caused by Alzheimer's disease, which is the most prevalent type. Vascular dementia, dementia with Lewy bodies, and frontotemporal dementia are the next most common types. In addition to having an impact on individuals, these illnesses place a heavy financial, emotional, and physical load on carers and healthcare systems [1].

Pharmacologic therapies will continue to rely on agents that have limited efficacy in alleviating the clinical symptoms seen in dementia patients (i.e., memantine for NMDA receptor antagonism and several cholinesterase inhibitors (e.g., donepezil, rivastigmine, galantamine) or those that are associated with side effects that frequently prohibit their use (e.g., hepatotoxicity, disorientation, and gastrointestinal upset). In addition, the limitations of monotherapy for dementia patients are being increasingly recognized relative to the complex pathology of dementia that encompasses amyloid-beta (Aβ) accumulation, tau hyperphosphorylation, and associated neuroinflammation and oxidative stress, as well as dysfunction of synaptic systems [2].

The efficacy of complementary therapy techniques including traditional herbal medicines is gaining increased attention by clinicians and scientists as an alternative method of providing symptomatic relief for memory and cognition. Systems of herbal formulation such as Ayurveda, Traditional Chinese Medicine (TCM), and Kampo contain bioactive herbal ingredients that contain naturally occurring phytochemicals that have pharmaceutical properties and have been used historically for improving cognition and sustaining memory. Evidence from preclinical studies supports that bioactive herbal chemistry including curcumin extracted from the rhizome of *Curcuma longa*, ginsenosides extracted from the root of *Panax ginseng*, and bacosides extracted from *Bacopa monnieri* exhibit antioxidant, anti-inflammatory, anti-amyloidogenic, and neuroprotective properties [3].

The purpose of this review is to critically assess the therapeutic potential of traditional herbal remedies and bioactive substances for the management of dementia. We will examine their mechanisms of action, evaluate the results of preclinical and clinical research, and discuss how these treatments might be integrated into contemporary neurodegenerative treatment paradigms. We hope to draw attention to the growing significance of plant-based therapies in addressing the complex biology of dementia with this synthesis [4].

Bioactive Compounds: Mechanisms and Sources

Types of bioactive compounds

Polyphenols

Polyphenols, a family of secondary plant compounds, have been shown to have neuroprotective effects against dementia.

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Curcumin, a diferuloylmethane from *Curcuma longa*, suppresses NF-κB-mediated cytokine production and activates the Nrf2 antioxidant pathway to control oxidative and inflammatory responses. In preclinical models, it has been shown to suppress the development of amyloid-beta (Aβ) plaques and enhance their removal by increasing macrophage-mediated phagocytosis. Red wine and grapes contain resveratrol, which activates sirtuin-1 (SIRT1), promoting mitochondrial biogenesis and improving neuronal survival. In transgenic Alzheimer's disease (AD) mice, resveratrol also reduces tau hyperphosphorylation and Aβ-induced cytotoxicity. The green tea catechin EGCG strongly destroys Aβ aggregation, chelates metals, and regulates apoptotic proteins, including Bcl-2 and Bax. Furthermore, EGCG promotes synaptic plasticity and inhibits the JNK signalling pathway, thereby producing its neuroprotective effects [5] (Figure 1).

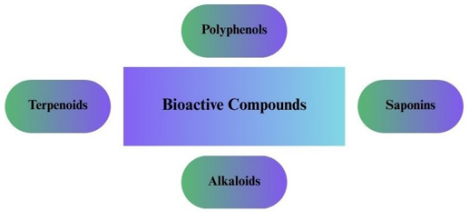

Figure 1. Types of bioactive compounds.

Alkaloids

Huperzia serrata is the source of Huperzine A, a sesquiterpene alkaloid that improves cholinergic transmission in the hippocampus by acting as a selective and reversible acetylcholinesterase (AChE) inhibitor. It also minimizes caspase-3-mediated apoptosis, maintains mitochondrial membrane potential, and attenuates glutamate-induced excitotoxicity in both in vitro and in vivo investigations. After receiving huperzine A, patients with mild-to-moderate AD showed improvements in their cognitive function, according to Chinese clinical trials [6].

Terpenoids

Terpenoids are recognized for their anti-apoptotic and antioxidant properties, especially ginkgolides and bilobalide from *Ginkgo biloba*. A standardized preparation of Ginkgo biloba extract (EGb 761), used in clinical settings, has demonstrated effectiveness in reducing neuropsychiatric symptoms and improving cognitive function in patients with dementia. While bilobalide stabilizes mitochondrial function and stimulates neurogenesis by upregulating BDNF, ginkgolides increase cerebral blood flow and block platelet-activating factor [7].

Saponins

The primary bioactive saponins in *Panax ginseng*, ginsenosides, have multimodal neuroprotective effects. Ginsenoside Rg1 decreases microglial activation, suppresses tau hyperphosphorylation, and improves synaptic plasticity. Rb1 modulates the PI3K/Akt and MAPK signaling cascades to shield neurons from oxidative damage. In animal models of AD, both substances have shown improved cognitive outcomes [8].

Mechanisms of action

Bioactive substances fight dementia in several ways: terpenoids and polyphenols lower inflammation and oxidative stress by increasing antioxidants such as glutathione and blocking cytokines such as TNF-α and IL-1β; alkaloids such as huperzine. Agents including curcumin, EGCG, and resveratrol reduce Aβ aggregation and facilitate its clearance, while A inhibits AChE and increases acetylcholine levels. By enhancing mitochondrial activity, stabilizing synaptic proteins such as PSD-95, and modulating apoptotic pathways through Bcl-2 family proteins, these substances also promote neuroprotection [9].

Pharmacokinetics and bioavailability challenges

Many bioactive substances have poor pharmacokinetics despite their promising pharmacodynamics. Curcumin, for instance, has little brain penetration, significant hepatic metabolism, and limited oral absorption. EGCG and resveratrol both have fast systemic elimination [10].

New delivery strategies are being investigated to improve therapeutic potential. In mouse models, curcumin-loaded PLGA nanoparticles, liposomal EGCG, and ginsenoside-encapsulated solid lipid nanoparticles have demonstrated increased bioavailability and brain-targeting effectiveness. These formulations prolong drug release, enhance blood-brain barrier permeability, and extend half-life. Transforming the preclinical efficacy of these bioactive substances into successful dementia treatments would require ongoing advances in nano-delivery and structural analog development. [11].

Traditional Herbal Medicine Systems

The use of plant-based medications in traditional herbal medicine is a well-established approach to promoting brain health and delaying cognitive decline associated with normal aging. This form of medicine typically has a basis in cultural and philosophical traditions, focuses on holistic approaches to care, and employs natural formulations that have been used for thousands of years within systems of medicine, such as Ayurveda, TCM, and other indigenous traditions, to maintain the balance of the mind-body connection and to provide neuroprotective benefits [12].

Ayurveda: Medhya rasayanas for cognitive rejuvenation

According to Ayurveda, the traditional medicine of India, Medhya Rasayanas are plants/plant-based compounds that may be utilized for their neuro-enhancing qualities related to memory and cognitive intelligence. Examples of plants that fit this description include; *Convolvulus pluricaulis* (Shankhpushpi), *Withania somnifera* (Ashwagandha), and *Bacopa monnieri* (Brahmi). Of these herbs, *Bacopa monnieri* has the greatest pharmaceutical activity, as its primary active ingredient, the compound bacoside, offers great value to neoroprotection and improved synaptic transmission. Numerous clinical studies have demonstrated that enhanced memory and increased concentration can be obtained from use by the elderly [13]. Ashwagandha, the second primary herb, contains a specific chemical compound called withanolide, which promotes neuroprotection by stimulating neurite outgrowth, reducing oxidative stress, and reducing the accumulation of Aβ (a protein implicated in the pathophysiology of Alzheimer's disease). The third primary herb, Shankhpushpi, acts as a nervine tonic, stimulating cognitive function by increasing acetylcholine levels in the hippocampus. The Guduchyadi Medhya Rasayana is a formulation that contains these three specific plant

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medications and has been shown to positively affect age-related declines in memory due to cognitive factors, while exhibiting an anti-stress effect. [14].

TCM: Harmonizing Qi for mental clarity

To support cognitive health, TCM emphasizes the harmony of Yin and Yang and the smooth flow of Qi, or vital energy. Key components of this system include *Salvia miltiorrhiza* (Danshen), *Panax ginseng*, and *Ginkgo biloba*. *Ginkgo biloba* is prized for its antioxidant protection and for increasing cerebral blood flow, which may improve cognitive function in people with dementia [15]. Ginsenosides in *Panax ginseng* have anti-inflammatory, neuroprotective, and antioxidant properties that enhance cognitive function. *Salvia miltiorrhiza* helps prevent and treat cognitive decline, especially vascular dementia, by improving blood circulation and reducing blood stasis. Within the TCM framework, these herbs are often combined in multi-herb regimens that target different aspects of cognitive health [16].

Other traditional systems: Holistic approaches to cognitive wellness

There are numerous uses of herbal medicine across various forms of medicine, such as Ayurvedic and TCM, to support cognitive function. An example of a formula from Japanese Kampo medicine that can be used to treat behavioral/psychiatric symptoms associated with dementia is Yokukansan. Similarly, in the holistic tradition of Unani medicine (practiced in regions of the Middle East and South Asia), herbal medicines such as *Bacopa monnieri* and Withania somnifera are prescribed for memory enhancement. Within African traditional medicine, native plants, such as *Securidaca longepedunculata*, are utilized for their potential neuroprotective effects; however, research continues to confirm this. Within Native American traditions, there are many forms of herbal medicine used to support mental/spiritual health. The diversity of methods for using herbal medicines underscores the need to integrate traditional knowledge with current scientific research to support the widely accepted use of herbal medicine for maintaining cognitive function [17].

Clinical and Preclinical Evidence Supporting Herbal Interventions in Dementia

Preclinical studies

The neuroprotective effects of plant-based substances in dementia are supported by several preclinical studies. Huperzine A, an alkaloid derived from *Huperzia serrata*, has demonstrated cognitive improvement in mouse models of Alzheimer's disease (AD) by reducing oxidative stress and Aβ formation, and by providing strong acetylcholinesterase inhibition. *Bacopa monnieri*, which is high in bacosides, improves learning and memory in mouse models by increasing cholinergic activity and lowering lipid peroxidation. In transgenic mice, curcumin from *Curcuma longa* has anti-inflammatory and anti-amyloidogenic properties by regulating NF-κB and reducing tau tangles and Aβ plaques. In animal models, *Ginkgo biloba* extract enhances cerebral perfusion and shields neurons from ischemic damage. These results demonstrate a variety of mechanisms that support their therapeutic potential, including antioxidant action, AChE inhibition, and modification of the amyloid pathway [18].

Clinical trials and meta-analyses

Clinical trials provide partial translational support. In a randomized controlled trial, *Ginkgo biloba* (EGb 761, 240 mg/day) reduced neuropsychiatric symptoms and improved cognition in adults with mild-to-moderate dementia. However, studies in healthy adults have produced contradictory results, likely due to variations in baseline cognition and trial design. In healthy older adults, 300 mg of *Bacopa monnieri* per day for 12 weeks has been shown to improve memory processing and acquisition. A meta-analysis has validated memory-boosting effects with few side effects. Due to its poor absorption, curcumin has demonstrated modest therapeutic effects despite its excellent preclinical efficacy. Bioavailable versions, such as Theracurmin, have shown promise in a recent experiment in which 18 months of supplementation reduced tau and Aβ deposits on PET imaging and enhanced memory and attention in non-demented people [19].

Synergistic Approaches: Herbal Formulations and Combination Therapy

Polyherbal formulations

Several herbs are combined in polyherbal preparations, which are essential to ancient medical systems like Ayurveda, to address different facets of cognitive decline. A polyherbal formulation including *Bacopa monnieri* (whole plant), *Hippophae rhamnoides* (leaves and fruits), and *Dioscorea bulbifera* (bulbils) was evaluated in patients with senile dementia of Alzheimer's type (SDAT) in a randomized, double-blind, placebo- and active-controlled clinical trial. Over a 12-month period, patients taking the polyherbal formulation (500 mg twice daily) showed significant improvements in Mini-Mental State Examination (MMSE) scores, digital symbol substitution, immediate and delayed word memory, attention span, and functional activity. These cognitive improvements were comparable to those seen with donepezil (10 mg twice daily), suggesting that the formulation may be effective in treating Alzheimer's disease-related cognitive decline [20].

The PI3K/Akt signalling pathway, which is essential for neuronal survival, synaptic plasticity, and memory formation, may be modulated to contribute to the neuroprotective benefits of such formulations. The pathophysiology of Alzheimer's disease has been linked to dysregulation of this pathway, resulting in tau hyperphosphorylation and amyloid-beta (Aβ) buildup [21].

Herb-drug combinations

A multimodal approach to treating dementia combines herbal medicines with traditional medications. In mouse models of Aβ-induced Alzheimer's disease, a study examined the combined effects of Environmental Enrichment (EE) and a Polyherbal formulation (BN). Compared with mice receiving either intervention alone, those receiving both BN (844 mg/kg body weight) and EE showed notable gains in cognition and spatial learning. Histopathological investigations found reduced amyloid plaque load and increased dendritic arborization, suggesting synergistic neuroprotective effects. According to these results, combining herbal remedies with conventional pharmaceutical treatments or lifestyle changes may improve treatment outcomes for Alzheimer's disease [22].

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Personalized and integrative medicine approaches

Integrative techniques combine traditional and alternative therapies for comprehensive care, whereas personalized medicine tailors' treatment to specific patient profiles. *Bacopa monnieri*, *Centella asiatica*, *Withania somnifera*, and *Convolvulus pluricaulis* are included in BR-16A (Mentat), a polyherbal formulation long used to improve cognitive abilities. Preclinical research showed that subchronic injection of BR-16A (100 mg/kg) enhanced memory retention and learning acquisition in rats with cognitive impairments caused by hypoxia, postnatal environmental deprivation, and prenatal undernutrition. The formulation's nootropic effects were comparable to those of the common cognitive enhancer piracetam. These findings highlight the value of customized treatment plans that incorporate herbal formulations with traditional medicines, as well as the potential of integrative and personalized medicine approaches in addressing cognitive decline [23].

Challenges and Future Directions

The effectiveness and reproducibility of herbal medicines for dementia are severely hindered by the lack of standardization across plant sources, extraction methods, and formulations. Standardization is aided by methods such as metabolomics and HPLC, yet regulatory oversight remains inadequate. Herbal safety is sometimes overstated; better pharmacovigilance is necessary, as contamination and herb-drug interactions pose serious risks. Technological advances such as nanotechnology enhance the bioavailability of phytochemicals, while network pharmacology and artificial intelligence help predict interactions and optimize combinations. To increase knowledge and guide the development of safe, effective treatments, future research should focus on large-scale, carefully monitored clinical trials, standardized extracts, and integrative "omics" [24].

Conclusion

Traditional herbal treatments contain bioactive components that can cure dementia and have encouraging neuroprotective properties. *Ginkgo biloba* has been shown to reduce oxidative stress and enhance cognition, particularly with the EGb 761 extract. In a randomized clinical trial, 240 mg of EGb 761 daily was found to be both safe and beneficial for patients with Alzheimer's disease. Similarly, in preclinical Alzheimer's models, curcumin (from *Curcuma longa*) reduces neuroinflammation and has anti-inflammatory and antioxidant properties.

Cognitive wellness has long been supported by traditional systems such as Ayurveda and TCM, but contemporary validation is crucial. To ensure safety and effectiveness, studies must use standardized extracts and follow regulated procedures. For example, contamination in certain Ayurvedic formulas has been found, underscoring the need for more stringent regulations.

Extensive research, oversight, and knowledge are needed to integrate herbal remedies into modern healthcare. Combining herbal remedies with traditional treatments could be beneficial, but clear guidance on dosage, interactions, and safety is essential. In conclusion, even if traditional herbal medicines have the potential to treat dementia, their successful integration into mainstream medicine will depend on robust clinical evidence and legal considerations. frameworks, and educational initiatives to ensure safe and effective use.

Disclosure Statement

No potential conflict of interest was reported by the author.

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