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ADVANCEMENTS IN NATURAL AND MODERN TREATMENTS FOR ALZHEIMER'S DISEASE IN PRECLINICAL AND EARLY STAGES

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ABSTRACT

Background: Alzheimer's disease (AD), the most common cause of dementia, is characterized by memory loss, cognitive decline, and behavioral changes. Current monoclonal antibodies raise concerns about cost and safety, despite modest disease-modifying effects. **Methodology:** Evidence from preclinical research, clinical trials, and meta-analyses on integrative methods for managing AD is compiled in this narrative review. We assessed natural phytochemicals (from plants like *Ginkgo biloba, Bacopa monnieri, Withania somnifera, Curcuma longa, and Salvia officinalis*), lifestyle modifications, and new technologies. With an emphasis on preclinical and early-stage AD data through 2025, standardized extracts such as EGb761 and saffron were given priority. **Results:** Certain plants' phytochemicals have anti-inflammatory, anti-amyloid, antioxidant, and neurotrophic properties that alter important AD pathways. Standardized extracts such as EGb761 and saffron have been shown in clinical trials to provide cognitive benefits comparable to those of prescription medications, with fewer side effects. Pharmacotherapy, natural modulators, stem cell therapy, AI-driven precision medicine, and other integrative strategies have shown promise in slowing disease progression. **Discussion:** Low bioavailability, formulation variability, and a lack of large-scale trials are some of the issues facing clinical translation. Natural remedies can complement modern treatments, particularly during the early stages of AD. Standardized formulations, sophisticated delivery methods, and thorough verification of synergistic strategies are essential for future success. **Conclusion:** Modern and natural therapies present promising options for managing AD at an early stage. Integrative care must be advanced through standardized formulations, enhanced delivery techniques, and robust clinical validation of synergistic approaches.

INTRODUCTION

Alzheimer's disease (AD) is the leading cause of dementia worldwide, accounting for 60–80% of all cases. It is a chronic, progressive neurodegenerative disorder characterized by memory loss, cognitive decline, and behavioral changes, which eventually impair an individual's ability to perform daily

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activities. As the global population ages, the incidence of AD continues to increase, creating significant personal, social, and economic burdens [1]. The most common cause of dementia globally is Alzheimer's disease (AD), which results in a gradual loss of cognitive function and places a substantial burden on both individuals and society. There is an opportunity for early intervention to slow or halt the progression of AD during its "preclinical" phase, marked by neuropathological features such as tau tangles and amyloid-beta accumulation, before clinical symptoms become evident [2-4].

Developing effective strategies for preclinical Alzheimer's disease requires understanding the early signs of the disease, the current treatment options, and emerging natural therapies. This preclinical stage, which can begin 10–20 years before clinical symptoms appear, presents one of the greatest challenges in AD treatment. Insidious pathophysiological changes, including oxidative stress, mitochondrial dysfunction, tau hyperphosphorylation, amyloid beta (Aβ) aggregation, and neuroinflammation, gradually damage brain structure and function during this period [5]. Preventing or delaying the progression to symptomatic AD depends on intervention during this early stage. Approved AD medications now available, including NMDA receptor antagonist memantine and acetylcholinesterase inhibitors (e.g., donepezil, galantamine, rivastigmine), give only limited symptomatic relief without changing the course of the disease. Monoclonal antibodies against Aβ plaques (such as aducanumab and lecanemab) have just been found to be disease-modifying drugs. But these therapies have limits, including high costs, little clinical benefit, and dangerous side effects like amyloid-related imaging abnormalities (ARIA) [6]. Also, their effectiveness seems better in the early stages, before AD develops, so it's really important to act quickly.

Given the complexity of AD pathogenesis and the drawbacks of current therapies, natural modulators have become increasingly appealing as either adjunct or alternative treatment choices. Preclinical studies have demonstrated neuroprotective benefits from a broad spectrum of plant-derived chemicals and dietary phytochemicals, achieved through antioxidant, anti-inflammatory, anti-amyloidogenic, and neurotrophic mechanisms. Among the most studied chemicals that can affect several AD pathogenesis pathways are polyphenols (e.g., curcumin, resveratrol), alkaloids (e.g., huperzine A, galantamine), and terpenoids (e.g., ginkgolides) [7].

Natural chemicals also offer advantages, including low toxicity, long-term safety, and synergistic mechanisms, which are particularly well-suited for preventive measures. Preclinical research has demonstrated that these chemicals restore synaptic plasticity, reduce neuropathological markers, and enhance cognitive function. Despite these encouraging results, their clinical use remains limited by issues such as low bioavailability, standardization, and a paucity of large-scale clinical studies. As illustrated in Figure 1, amyloid and tau abnormalities precede overt cognitive decline by many years, underscoring the rationale for targeting preclinical and early symptomatic stages with both pharmacological and natural modulators. It also summarizes the hypothetical sequence of biomarker and clinical changes across the preclinical, MCI, and dementia stages of AD, adapted from Jack et al., with permission. It illustrates the widening window for preclinical and early-stage intervention emphasized throughout this review.

Although there are several thorough reviews of Alzheimer's disease, this manuscript purposefully limits its scope to three main goals: (i) to investigate the mechanisms of cognitive decline in the preclinical and early symptomatic stages of AD, including subjective cognitive decline (SCD) and mild cognitive impairment (MCI); (ii) to critically assess integrative strategies and natural modulators with a particular emphasis on evidence in preclinical, at-risk, or early-stage populations, clearly distinguishing these from data in mild-to-moderate dementia; and (iii) to identify translational gaps that need to be filled for future therapeutic success, especially barriers in moving from preclinical models to early-intervention trials.

METHODS

This review was conducted as a structured narrative review with elements of a scoping approach, rather than as a formal systematic review. Electronic searches were performed in PubMed/MEDLINE, Scopus, Web of Science, and Google Scholar for articles published between January 2000 and September 2025 using combinations of the keywords "Alzheimer's disease", "preclinical Alzheimer's", "subjective cognitive decline", "mild cognitive impairment", "phytochemicals", "medicinal plants", "integrative medicine", "lifestyle intervention", "monoclonal antibody", and "disease-modifying therapy". Priority was given to human randomized controlled trials and large observational studies in preclinical, at-risk, and early-stage AD populations, followed by high-quality preclinical (in vitro and in vivo) mechanistic work

relevant to early pathophysiology. Inclusion criteria were: (i) clear diagnosis or characterization of AD, MCI, or preclinical/at-risk states; (ii) evaluation of pharmacological, phytochemical, lifestyle, or technology-based interventions; and (iii) reporting of cognitive or biomarker outcomes. Case reports, single-arm studies without objective outcomes, and non–peer-reviewed sources were generally excluded unless they provided unique mechanistic insights. Because this was not a formal systematic review, no quantitative meta-analysis was undertaken; instead, the quality of evidence was judged qualitatively based on study design, sample size, duration, and risk of bias as reported in the original publications. Throughout the manuscript, phrases such as "mounting evidence" or "recent evidence increasingly highlights" are reserved for areas supported by multiple independent studies or higher-level evidence (e.g., systematic reviews and meta-analyses).

Preclinical Stages and Early Cognitive Decline in Alzheimer's Disease

In the following sections, evidence is explicitly separated, wherever possible, into (a) preclinical/at-risk cohorts (biomarker-positive, SCD, MCI) and (b) patients with mild-to-moderate AD dementia, to maintain the intended focus on early stages. Many studies have shown that in Alzheimer's disease (AD), cognitive loss starts many years before the onset of clinical signs. A biomarker-based framework has been proposed to characterize AD as a biological continuum, in which amyloid-beta (Aβ) and tau pathologies silently accumulate during the preclinical phase [1]. This idea supports the present knowledge that cognitive impairment follows neuropathological changes; hence, early diagnosis is a key area of attention in AD research. The preclinical phase of Alzheimer's disease has been conceptually divided into three phases: (1) asymptomatic Aβ accumulation, (2) Aβ pathology with early signs of neurodegeneration, and (3) slight cognitive decline accompanied by biomarker abnormalities [2]. The third phase corresponds to the notion of conceptual cognitive decline, defined as early, measurable changes in cognitive performance that do not yet meet the criteria for mild cognitive impairment (MCI). This underscores the need for more sensitive diagnostic instruments that integrate cognitive tests with biomarker information. Although cognitively normal at baseline, people with high Aβ burden frequently show steady deterioration in executive functioning and episodic memory over time [3]. Healthy elderly people with high Aβ levels have subtle cognitive impairments, which shows that neuropathological changes have a measurable effect on cognition even before clinical thresholds are reached [4]. Subjective cognitive decline (SCD), or self-reported cognitive symptoms despite normal performance on standard neuropsychological testing, has been identified as a possible early sign of preclinical AD. It is now often thought of as a transitional state that could come before both mild cognitive impairment (MCI) and dementia [5,6]. Studies show that roughly 25% of people with SCD advance to MCI within four years. Those who test positive for AD biomarkers, such as tau protein or amyloid beta deposition on neuroimaging or in cerebrospinal fluid, have a substantially greater risk [7, 8]. These results highlight the need for SCD as a diagnostic indicator that can improve early detection of persons at risk for AD progression.

Differentiating typical cognitive aging from preclinical Alzheimer's disease remains problematic. Although age-related decline typically affects processing speed and working memory, it progresses more slowly and less severely than AD-related decline [9]. However, studies that combine biomarker findings with changes in people's thinking over time have shown that if there was more Aβ and tau in the brain early on, it was more likely that their cognitive abilities would decline more rapidly. This suggests that cognitive problems in preclinical Alzheimer's disease may have a pathological cause. Sensitive cognitive tools have been developed from large multicenter studies to track this early decrease. The Preclinical Alzheimer's Cognitive Composite (PACC), a composite scoring system, has been developed to identify small but consistent changes in memory and executive function over time in individuals with biomarker-positive Alzheimer's disease [10,11]. Early-phase clinical studies focusing on people at risk of AD now often use these tools. Also investigated is the idea of cognitive reserve to account for inter-individual variation in the presentation of cognitive impairment. Higher educational, occupational, or intellectual involvement may help people endure more neuropathology before manifesting clinical indications, thereby obscuring early declines and complicating diagnosis in the preclinical stage [12]. The body of research as a whole indicates that in the early phases of Alzheimer's disease, conceptual and subjective cognitive impairment are relevant phenomena. Early identification and prevention techniques are improved by combining self-reported cognitive changes, objective cognitive measures, and biomarker profiles, therefore stressing their need.

Neuroprotective Medicinal Plants for Alzheimer's Disease

Multiple mechanisms, including antioxidant activity, cholinesterase inhibition, inhibition of amyloid-β aggregation, anti-inflammatory effects, and enhancement of synaptic plasticity, have been shown in several medicinal plants to promote neuroprotective effects against Alzheimer's disease (AD). Key pathological characteristics of AD, such as oxidative stress, neuroinflammation, amyloid plaque formation, and neurotransmitter imbalance, are targeted by these phytochemicals. *Clitoria ternatea* also contributes via antioxidative pathways and cholinergic modulation. Table 1 lists key medicinal plants with neuroprotective potential in AD, along with information on their active ingredients, modes of action, and supporting experimental data**.**

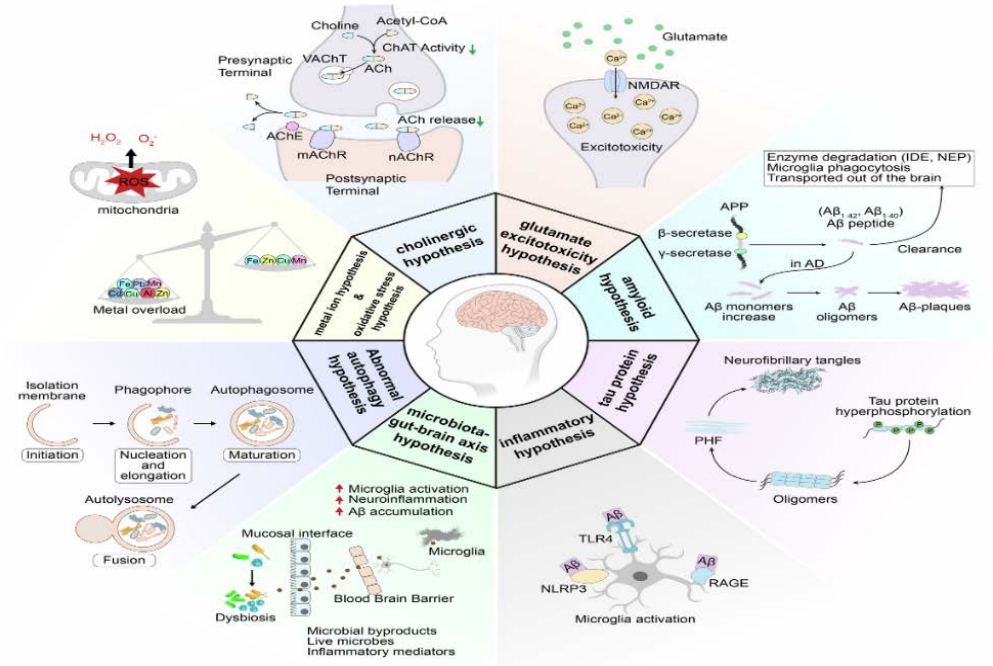

Figure 1: Neurodegenerative Cascade in Alzheimer's Disease

Table 1: Medicinal Plants with Neuroprotective Activity in Alzheimer's Disease, stratified by study type and disease stage

Plant (Latin name)	Active compounds	Primary mechanisms of action	Study type (in vitro / animal/ human)	Population/stage (healthy, at-risk, MCI, AD)	Key outcome measures	Ref.
Ginkgo biloba	Flavonoids, ginkgolides	Antioxidant, anti-amyloid, neurovascular protection	Human RCTs; observational; animal models	Mild-to-moderate AD; mixed dementia; limited data in MCI/at-risk populations	Modest improvement in cognition and activities of daily living versus placebo; mixed results across trials	[13]
Bacopa monnieri (Brahmi)	Bacosides A, B	Synaptic repair, antioxidant, and cholinergic modulation	Human RCTs; animal models	Elderly with age-associated memory impairment; limited data in MCI/early AD	Improved memory and attention scores versus placebo in some trials	[14]
Withania somnifera (Ashwagandha)	Withanolides	Aβ clearance, neurogenesis, anti-inflammatory	Animal models; early-phase human studies	APP/PS1 AD mice; small human samples with cognitive complaints	Reduced Aβ burden, improved learning and memory in mice	[15]
Curcuma longa (Turmeric)	Curcumin	Anti-amyloid, anti-inflammatory, antioxidant	In vitro; animal models; small human trials	Transgenic AD mice; older adults with cognitive decline	Inhibition of Aβ aggregation; improved memory in animal models; inconsistent human cognitive	[16]

					outcomes; constrained by poor bioavailability	
Centella asiatica (Gotu Kola)	Asiaticoside, madecassoside	Cholinesterase inhibition, antioxidant, anti-amyloid	In vitro; animal models	Scopolamine-induced amnesia; Aβ toxicity models	Protection against Aβ-induced neurotoxicity; improved learning and memory	[17]
Panax ginseng	Ginsenosides	Neurotransmitter regulation, anti-inflammatory	Human RCTs; animal models	Mild-to-moderate AD; cognitive impairment in older adults	Improved cognitive scores with adjunctive use; reduced Aβ in preclinical models	[18]
Salvia officinalis (Sage)	Rosmarinic acid, essential oils	AChE inhibition, antioxidant, anti-inflammatory	Human RCTs; animal models	Mild-to-moderate AD; healthy volunteers	Improved attention and memory versus placebo; reduced agitation in some studies	[19]
Clitoria ternatea	Ternatins, anthocyanins	Antioxidant, cholinergic modulation	Animal models	Scopolamine-induced amnesia; normal rats	Enhanced hippocampal ACh content and memory performance	[20]
Crocus sativus (Saffron)	Crocin, safranal	Anti-amyloid aggregation, NMDA antagonism, antioxidant	Human RCTs; animal models	Mild-to-moderate AD	16-week RCTs show similar short-term cognitive outcomes to donepezil with better tolerability; no data in preclinical AD	[21]
Melissa officinalis (Lemon balm)	Rosmarinic acid	AChE inhibition, anxiolytic	Human RCTs	Mild-to-moderate AD; healthy adults	Improvement in agitation and modest cognitive benefit versus placebo	[22]
Camellia sinensis (Green tea)	EGCG	Anti-amyloid, anti-inflammatory, antioxidant	In vitro; animal models	Aβ-induced neurotoxicity models; dementia models	Reduced oxidative stress and AChE activity; attenuation of Aβ-induced neuronal damage	[23]
Berberis vulgaris (Berberine)	Berberine	AChE inhibition, anti-amyloid, metabolic modulation	Animal models, systematic review of preclinical/ early clinical data	AD rodent models; early-phase human metabolic studies	Reduced cognitive deficits and Aβ pathology in animal models; potential relevance for metabolic risk factors	[24]
Tinospora cordifolia	Tinosporine, alkaloids	Antioxidant, anti-inflammatory	Animal models	Scopolamine-induced cognitive impairment	Improved learning and memory performance	[25]
Zingiber officinale (Ginger)	Gingerols, shogaols	Anti-inflammatory, antioxidant, anti-Aβ	Human RCTs; animal models	Middle-aged healthy women; animal AD models	Improved working memory and reaction time in healthy women; enhanced neurogenesis and memory in animals	[26]

Current Therapeutics Targeting Preclinical and Early Alzheimer's Disease

Symptomatic Treatments

Cholinesterase inhibitors and NMDA receptor antagonists are two approved symptomatic treatments that primarily alter neurotransmission (Table 2). These medications offer some relief, but they don't deal with the underlying causes of the illness [27-30].

Disease-Modifying Therapies (DMTs)

Recent FDA-approved monoclonal antibodies such as aducanumab and lecanemab target aggregated amyloid-beta and have demonstrated substantial reductions in amyloid PET signal,

particularly in patients with MCI due to AD or mild AD dementia enrolled in phase III trials. Clinically, these agents produce a modest slowing of decline on global cognitive and functional scales (e.g., differences of approximately 0.45-0.5 points on CDR-SB over 18 months compared with placebo), which, although statistically significant, represent small absolute changes at the individual level. Amyloid-related imaging abnormalities (ARIA-E and ARIA-H) occur in a meaningful proportion of treated patients, especially APOE ε4 carriers, necessitating MRI monitoring and careful risk–benefit assessment. These therapies are therefore best conceptualized as early-stage disease-modifying options for carefully selected, biomarker-positive patients, rather than as broadly applicable treatments across the AD continuum. [31,32].

Table 2: Approved symptomatic treatments for alzheimer's disease: mechanisms and indications

Drug	Mechanism	Indication	Ref.
Rivastigmine	Cholinesterase inhibitor	Mild-moderate AD	[27]
Donepezil	Cholinesterase inhibitor	Mild-severe AD	[28]
Memantine	NMDA receptor antagonist	Moderate-severe AD	[29]
Galantamine	Cholinesterase inhibitor	Mild-moderate AD	[30]

Integrative and Future Strategies for Alzheimer's Disease Management

Given the multifactorial etiology and progressive nature of Alzheimer's disease (AD), an integrative approach combining pharmacological, natural, and lifestyle-based treatments shows more promise than monotherapy [33]. Evidence from multidomain intervention trials, such as those that combine diet, exercise, cognitive training, and vascular risk management in at-risk older adults, suggests that integrated lifestyle programs can attenuate cognitive decline, particularly among individuals at elevated risk of dementia. Although few studies have formally combined nutraceuticals with approved AD drugs, emerging data support the feasibility of add-on use of standardized extracts (e.g., Ginkgo, ginseng) alongside cholinesterase inhibitors, with acceptable safety and potential additive cognitive benefits. Figure 3 proposes a pragmatic clinical algorithm in which (i) biomarker- and risk-based stratification identifies preclinical and early-stage patients; (ii) all patients receive structured multidomain lifestyle intervention; and (iii) pharmacotherapy & selected evidence-based phytochemicals are layered according to disease stage, comorbidities, and patient preferences.

Safety, tolerability, and herb–drug interactions

Although many medicinal plants discussed in this review are perceived as having "low toxicity" and "long-term safety", systematic data on adverse events and herb–drug interactions in AD populations remain limited. *Ginkgo biloba* extracts, for example, are generally well tolerated but have been associated with an increased risk of bleeding when combined with anticoagulants or antiplatelet agents, which is clinically relevant in older patients frequently receiving such medications.

Saffron and *Bacopa monnieri* are typically associated with mild gastrointestinal symptoms and occasional headache in short-term trials, but robust long-term safety data beyond 6–12 months are lacking. Potential pharmacodynamic interactions with cholinesterase inhibitors (e.g., additive cholinergic effects for *Bacopa, Melissa officinalis*) & pharmacokinetic interactions via CYP450 modulation (e.g., *Ginkgo*, berberine-containing plants) should be carefully considered when designing integrative regimens. Future trials should systematically capture adverse event profiles, interaction signals, and contraindications to support safe translation into routine practice.

Synergy in Combined Interventions

Preservation of cognitive function & reversing neurodegeneration depend on the synergistic effects of natural treatments, conventional medicines, and lifestyle changes. Research shows that good lifestyle choices, including regular physical activity, cognitive training, and a Mediterranean diet, help lower the chance of developing Alzheimer's disease [34-36]. Aerobic activity increases brain perfusion & hippocampal neurogenesis. Cognitive training strengthens synaptic resistance [35]. The Mediterranean diet protects against neurodegenerative disorders by providing antioxidants and anti-inflammatory vitamins [36].

Significance of Natural Materials

Preclinical and some clinical studies show that plant-derived bioactives like curcumin, resveratrol, *Ginkgo biloba*, and several flavonoids have antioxidant, anti-inflammatory, anti-amyloid, and neurotrophic effects. These natural modulators may improve overall effectiveness and slow disease progression in early-stage or at-risk populations when used alongside traditional treatments [37-41].

Individualized, Precision-Based Treatment

Personalized medicine driven by biomarker profiling, including APOE ε4 genotype, CSF amyloid-beta, phosphorylated tau, and neuroimaging biomarkers, enables focused prevention and treatment approaches [42].

Integrating Technology

Early detection, real-time tracking, and timely adaptation of tailored interventions are made possible by developments in digital cognitive testing, wearables, and AI-based analytics [48].

PROSPECTS FOR THE FUTURE

Future control of Alzheimer's disease depends on accuracy, prevention, and customization. Integrative approaches combining biomarkers and digital technologies, as well as multidomain lifestyle interventions & natural neuroprotective substances, can improve early identification and long-term management [25,33]. Clinical validation of synergistic strategies, including the combination of anti-amyloid medicines with anti-inflammatory phytochemicals and dietary changes, is necessary, particularly in low-resource countries [38,39]. The creation of safe, consistent, and bioavailable natural compound compositions, such as nano-formulated curcumin and resveratrol analogues, may improve therapeutic translation [37,38].

Accumulation of Amyloid-beta (Aβ) and Tau Protein

The buildup of amyloid-beta plaques and tau tangles is a key part of the pathology of Alzheimer's disease (AD). Natural products like curcumin, which comes from turmeric, have shown promise in reducing amyloid plaque formation and stopping tau aggregation by acting as antioxidants and anti-inflammatory agents. This is similar to the dual-targeting strategy used in new drug development. Resveratrol and green tea catechins are two other polyphenols that have been shown to work against amyloid and tau pathology. This supports the idea of creating natural agents that target multiple diseases [16,41].

Modulation of Neuroinflammation

The progression of AD is significantly influenced by chronic neuroinflammation. Numerous natural substances, including extracts from *Salvia officinalis*, caffeoylquinic acids in *Centella asiatica*, and ginsenosides from Korean red ginseng, have been shown to exhibit anti-inflammatory properties targeting cytokine suppression and microglial activation. These substances may act as modulators of neuroinflammatory pathways, thereby enhancing the efficacy of synthetic drug candidates targeting TREM2 activation and IL-1β suppression [17,18,21].

CRISPR and Gene Therapy

Certain natural compounds may exert epigenetic regulation, influencing gene expression involved in AD, even though gene-editing techniques like CRISPR are state-of-the-art for targeting genetic risk factors such as the APOE gene. For instance, substances such as green tea's EGCG (epigallocatechin gallate) have been shown to alter neuroprotective gene expression, suggesting that gene editing and phytochemicals may work in tandem to treat AD in the future [23,45].

Stem Cell Treatment

The goals of stem cell therapy are cognitive restoration and neuronal replacement. Various natural products, including alkaloids and flavonoids, can improve neural stem cell survival, proliferation, and differentiation. By fostering an environment conducive to brain regeneration and repair, these organic bioactives may help with stem cell therapy [46].

Neuroprotection and Synaptic Plasticity

To stop cognitive decline, agents that enhance synaptic plasticity & offer neuroprotection are essential. It has been demonstrated that natural remedies like *W. somnifera, G. biloba* & *B. monnieri* improve neurotransmitter levels, synaptic function, and antioxidant defenses. These activities support cognitive abilities and neuronal health, which is consistent with future medication objectives of enhancing synaptic resilience [13-15,38,47].

Artificial Intelligence (AI) for Personalized Treatment

Personalized medicine powered by AI has the potential to improve the treatment of AD. AI may help match particular natural compounds or herbal formulations to patient profiles based on genetics, biomarkers, and cognitive status, combining traditional knowledge with precision medicine. This is helpful given the variety of effects of natural products and patient variability [48].

Early Identification and Proactive Treatments

For AD to be effectively treated, early intervention is essential. Imaging, biomarkers, and cognitive tests are being employed to improve these early diagnostic instruments, thereby enabling the development of more potent prophylactic treatments that delay

symptom onset [43,49]. At present, AI-driven personalization of herbal formulations and biomarker-guided matching of phytochemicals to individual patients remain largely conceptual, supported mainly by proof-of-concept models and retrospective analyses rather than prospective clinical trials. Similarly, CRISPR-based strategies targeting AD-related genes (e.g., APOE) and stem-cell-supporting phytochemicals are still in preclinical or very early human research, with no approved applications for AD treatment. These approaches should therefore be viewed as hypothesis-generating and future-oriented, rather than near-term therapeutic options for current patients.

DISCUSSION

The specific goals previously mentioned, namely, assessing the function of natural modulators and integrative strategies in early-stage AD management, form the basis of this conversation. To avoid redundancy with the introduction and earlier sections, this discussion focuses on integrating preclinical mechanisms, clinical evidence in preclinical/early AD, and translational gaps in implementing integrative strategies, rather than re-listing all mechanisms and agents. The emphasis here remains on early intervention techniques and their translational value, rather than on thorough reviews. Overall, the strength of clinical evidence for these botanicals remains modest compared with licensed AD drugs, with most trials characterized by small sample sizes, single-center designs, short durations, and heterogeneous outcome measures. Dose-response relationships are often poorly defined, and many positive findings come from preclinical models using concentrations that exceed those achievable with standard oral dosing in humans. These factors, along with variable extract standardization, likely contribute to the frequent discrepancy between promising mechanistic data and the relatively small cognitive gains observed in clinical trials. Recent evidence increasingly highlights the therapeutic potential of medicinal plants and their phytochemicals in the management of Alzheimer's disease, providing multi-target neuroprotective actions that address the disorder's complex pathogenesis [37-41].

Unlike conventional pharmacotherapies such as acetylcholinesterase inhibitors and NMDA receptor antagonists, which predominantly offer symptomatic relief through single-target mechanisms, plant-derived agents modulate multiple interlinked pathological pathways central to AD progression [37,38,41]. Key botanicals, including *Ginkgo biloba, Bacopa monnieri, Withania somnifera, Curcuma longa, Panax ginseng, Centella asiatica, and Salvia officinalis*, demonstrate a broad pharmacodynamic profile encompassing.

Inhibition of amyloid-beta aggregation and promotion of its clearance [37,39]. Reduction of tau hyperphosphorylation and prevention of neurofibrillary tangles [38,40]. Modulation of neuroinflammation by suppressing pro-inflammatory cytokines and the NF-κB pathway [37,39]. Enhancement of antioxidant defenses through increasing endogenous enzymes like superoxide dismutase and catalase [38,40]. Improvement of cholinergic neurotransmission via acetylcholinesterase inhibition [39]. Promotion of synaptic plasticity and neurogenesis by upregulating BDNF and other synaptic proteins [40,41]. To link mechanistic pathways and specific interventions more explicitly, Figure 1 presents a matrix mapping major AD pathophysiological processes (Aβ accumulation, tau hyperphosphorylation, neuroinflammation, oxidative stress, synaptic dysfunction) against selected pharmacological agents, phytochemicals, and lifestyle interventions, along with an approximate level of evidence (preclinical only vs early clinical vs multiple RCTs). This matrix underscores that most natural products currently have strong preclinical support across several pathways but only limited early-stage clinical data. In contrast, monoclonal antibodies show robust effects on amyloid biomarkers yet relatively modest clinical benefit, highlighting complementary rather than interchangeable roles in integrative early-intervention strategies.

Standardized extracts such as *Ginkgo biloba EGb761, Crocus sativus* (saffron), and *Bacopa monnieri* have shown measurable but modest cognitive benefits in randomized controlled trials, typically in mild-to-moderate AD or age-associated cognitive decline, with effect sizes in the small-to-moderate range and treatment durations of 3–12 months. For example, in a 16-week, randomized, double-blind trial in mild-to-moderate AD ($n \approx 50$–60 per arm), saffron (30 mg/day) produced ADAS-Cog and CDR-SB changes that were statistically comparable to donepezil (10 mg/day). Still, the trial was single-center, short-term, and limited to mild-to-moderate dementia, which constrains generalizability and does not establish equivalence in long-term outcomes or in preclinical/at-risk populations. Similarly, meta-analytic data suggest that EGb761 may confer small improvements in cognition and activities of daily living in

dementia. Still, most trials include patients with established disease rather than preclinical AD [38,39,41]. For instance, saffron has performed similarly to donepezil in mild-to-moderate AD, with better tolerability [39]. Likewise, preclinical studies with withanolide-rich *Withania somnifer*a extracts and curcumin from *Curcuma longa* report reductions in Aβ burden, suppression of oxidative stress, and improved synaptic integrity [37,38,40].

However, translating these findings into mainstream therapy faces challenges, including variable extract quality, batch-dependent phytochemical profiles, poor bioavailability of certain compounds (e.g., curcumin), and a lack of well-powered, multicenter randomized controlled trials. Safety profiles are generally favorable, but long-term safety and herb-drug interaction studies are still limited. For compounds such as curcumin and resveratrol, typical oral bioavailability is low, resulting in plasma and brain concentrations that are far below those used in many in vitro and animal studies, where micromolar exposures are common. Nano-formulations, phospholipid complexes, and structural analogues have been developed to enhance absorption and brain penetration; however, most remain at the preclinical or early phase I/II clinical trial stage, and large, multicenter RCTs powered for clinical outcomes in preclinical or early AD are still lacking. Future trials should incorporate pharmacokinetic–pharmacodynamic modeling, standardized formulations, and biomarker-anchored endpoints to better link target engagement to cognitive benefit and facilitate regulatory acceptance [38,41]. Mounting evidence suggests that integrative regimens combining natural products, pharmacological therapy, and lifestyle modification offer synergistic neuroprotection. Nutritional strategies like the Mediterranean diet, regular aerobic exercise, and cognitive training contribute to brain resilience, partly by enhancing hippocampal neurogenesis, improving cerebrovascular function, and modulating oxidative and inflammatory status [34-36].

The advent of precision medicine provides an opportunity to target interventions based on genetic risk (e.g., APOE ε4 allele status), fluid biomarkers (Aβ42, p-tau), and neuroimaging data [42]. Such stratification allows early, personalized intervention in at-risk or preclinical populations where neuroprotective phytochemicals may have the greatest impact [40,41]. Digital health technologies and AI-driven analytics now enable continuous cognitive monitoring and adaptive treatment strategies, increasing the feasibility of dynamic, long-term integrative care models [43,44].

CONCLUSION

The diverse neuroprotective potential of medicinal plants in Alzheimer's disease (AD) is highlighted by mounting evidence from recent preclinical and clinical trials. The current review highlights the important antioxidant, anti-inflammatory, anti-amyloid, and neurotrophic properties of species such as *Ginkgo biloba*, *Bacopa monnieri*, *Withania somnifera*, *Curcuma longa*, *Panax ginseng*, *Centella asiatica*, and *Salvia officinalis*. All of these results suggest that phytochemicals may influence several AD pathological targets, including tau hyperphosphorylation, oxidative stress, amyloid-beta aggregation, cholinergic dysfunction, and synaptic degeneration. These plant-based compounds have a broad-spectrum therapeutic profile that aligns with the multifactorial nature of AD, in contrast to traditional single-target medications.

This review acknowledges several limitations, including the low bioavailability of some compounds (such as curcumin), variation in phytochemical content, the paucity of large-scale, multicenter clinical trials, and the lack of adequate long-term safety data. Translating these encouraging results into clinical applications will require filling these gaps with standardized formulations, sophisticated nanocarrier-based delivery systems, and carefully planned randomized clinical trials. The study of medicinal plants offers a sustainable, cost-effective, and biologically diverse path toward developing safer, more potent neuroprotective interventions in the current environment, where AD remains a global health concern with limited therapeutic success [38,39].

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NIL

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTION

Latha S conceptualized the topic and conducted the comprehensive review, including literature collection, data interpretation, and manuscript drafting. Ronald Darwin C critically reviewed the manuscript, provided intellectual input, and made necessary corrections to improve its clarity and

scientific quality. Both authors read and approved the final version of the manuscript for submission and publication.

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