Journal of Molecular and Pharmaceutical Sciences

Review

Natural products in Alzheimer's disease: a review of promising neuroprotective agents

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Abstract

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by cognitive decline, memory impairment, and neuronal loss, representing a major global health challenge. Current therapeutic strategies, including acetylcholinesterase inhibitors, provide only symptomatic relief and are often associated with adverse effects, highlighting the need for safer and more effective alternatives. In this context, plant-derived bioactive compounds have gained considerable attention due to their diverse pharmacological properties and multi-target mechanisms of action. This review explores the potential of natural metabolites, including polyphenols, alkaloids, terpenoids, fatty acids, vitamins, and minerals, in the prevention and management of AD. These compounds exhibit neuroprotective effects through antioxidant, anti-inflammatory, anti-amyloidogenic, and anticholinesterase activities, as well as modulation of key cellular signaling pathways. Additionally, the role of modern approaches such as metabolomics, in silico screening, artificial intelligence, and integrated multi-omics strategies in accelerating the discovery and characterization of bioactive molecules is discussed. Collectively, these advances highlight the promising potential of natural compounds as innovative and safer therapeutic agents for Alzheimer's disease, paving the way for the development of more effective and personalized treatment strategies.

Keywords:

Alzheimer's disease, natural products, neuroprotection, biomolecules, molecular docking, metabolomics.

★ Received May 04, 2026; accepted June 04, 2026

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Cited as: Srief M, Srief M.L. Natural products in Alzheimer's disease: a review of promising neuroprotective agents. J. Mol. Pharm. Sci. 05 (01), 2026, 19-28.

1. Introduction

Human health has always been considered a fundamental priority for socio-economic progress, particularly in light of the emergence of numerous chronic diseases and the global spread of pandemics. To combat these conditions, medications are used for prevention, treatment, and sometimes diagnosis, relying on active substances combined with excipients that enable drug formulation. However, the concept of an ideal drug that exclusively targets a specific health problem without any side effects does not exist. Medications may cause undesirable side effects, the risk of which depends on the drug used, its mode of administration, potential drug interactions, and patient-specific characteristics [1].

Alzheimer's disease is one of the chronic conditions that poses significant challenges to society, particularly in terms of healthcare resources and its impact on patients' quality of life and that of their families. This disease is a progressive neurological disorder characterized by impairments in memory, language skills, judgment, and orientation. Each year, approximately 360,000 new cases are diagnosed, corresponding to about 980 new cases per day or 40 per hour. If this trend continues, the number of affected individuals could quadruple over the next 50 years. The cost of treatment and care has steadily increased, reaching 150 billion dollars in 2014, 236 billion in 2016, and 277 billion in 2018 [2].

Current treatments for Alzheimer's disease, particularly acetylcholinesterase inhibitors such as Donepezil, Rivastigmine, and Galantamine, are widely used in clinical practice. However, despite their relative effectiveness, these treatments are associated with several adverse effects, including fatigue, vomiting, and dizziness [3,4,5,6]. These limitations, combined with the progressive nature of the disease and the high cost of care, have prompted researchers to explore safer and better-tolerated therapeutic alternatives.

In this context, natural metabolites derived from medicinal plants represent a promising source of new bioactive molecules. Several studies have highlighted compounds capable of inhibiting both acetylcholinesterase and butyrylcholinesterase, including alkaloids, flavonoids [7], and phenolic acids [8,9].

Furthermore, the integration of modern approaches such as molecular docking allows the prediction of interactions between ligands and biological targets, as well as the three-dimensional structure of the resulting complexes, thereby facilitating the discovery of new therapeutic agents [10]. In addition, encapsulation techniques improve the stability and protection of bioactive compounds, enhancing their potential for the development of innovative treatments [11].

In this context, this review aims to highlight the promising role of natural metabolites as potential therapeutic agents against Alzheimer's disease, by thoroughly exploring their mechanisms of action, structural diversity, their ability to target multiple pathological pathways simultaneously, and integrating emerging computational and multi-omics approaches compared with previous reviews.

2. Pathophysiology of Alzheimer's Disease

Alzheimer's disease (AD) causes major lesions, notably neurofibrillary degeneration and senile plaques, which affect regions such as the hippocampus and the associative cortex. These lesions (Figure 1) are responsible for the neuronal degeneration characteristic of the disease [12].

2.1. Neurofibrillary Degeneration (NFD)

Neurofibrillary degeneration (NFD) is caused by the abnormal accumulation of hyperphosphorylated Tau proteins within neurons. Under normal conditions, Tau proteins are involved in maintaining the structure of microtubules, which play a crucial role in signal transmission from the neuronal cell body to the synapse. In pathological conditions, Tau detaches from microtubules due to alterations in its metabolism, particularly its phosphorylation state, which is essential for regulating its function.

In Alzheimer's disease, the abnormal accumulation of phosphorylated Tau disrupts axonal transport, leading to a sequential progression of lesions in different brain regions, beginning with the hippocampus (a region responsible for the formation and storage of long-term memory). Consequently, the cytoskeleton disintegrates and can no longer be maintained. Tau proteins aggregate into filaments that lose their ability to stabilize microtubules. The accumulation of these filaments constitutes neurofibrillary degeneration, ultimately leading to neuronal death and loss of synaptic connections [13].

2.2. Senile Plaques

Senile plaques are characterized by the accumulation of amyloid deposits at their core, composed of degenerated dendritic fragments and astrocytes [13].

At the surface of neurons (cell membrane), there is a large protein known as amyloid precursor protein (APP), which plays a protective role and participates in neuronal self-repair. Under normal conditions, APP—containing a β-amyloid domain—is cleaved by two enzymes: β-secretase and γ-secretase. This process releases β-amyloid peptides, which are subsequently degraded in the body [14].

In Alzheimer's disease, a pathological imbalance occurs: APP is produced in excessive amounts and aggregates into insoluble fibrils, forming senile plaques. The accumulation of β-amyloid increases the production of free radicals and initiates a cascade of events leading to cell death, including activation of apoptotic pathways, lipid peroxidation, and disruption of cellular membranes. It also exerts chemoattractant and activating effects on monocytes and astrocytes, resulting in cytokine release and the initiation of an inflammatory cascade [15,16]. The presence of these two types of lesions is essential for the development of Alzheimer's disease, which is also characterized by significant brain atrophy and, at the neurobiological level, a decrease in acetylcholine production [16].

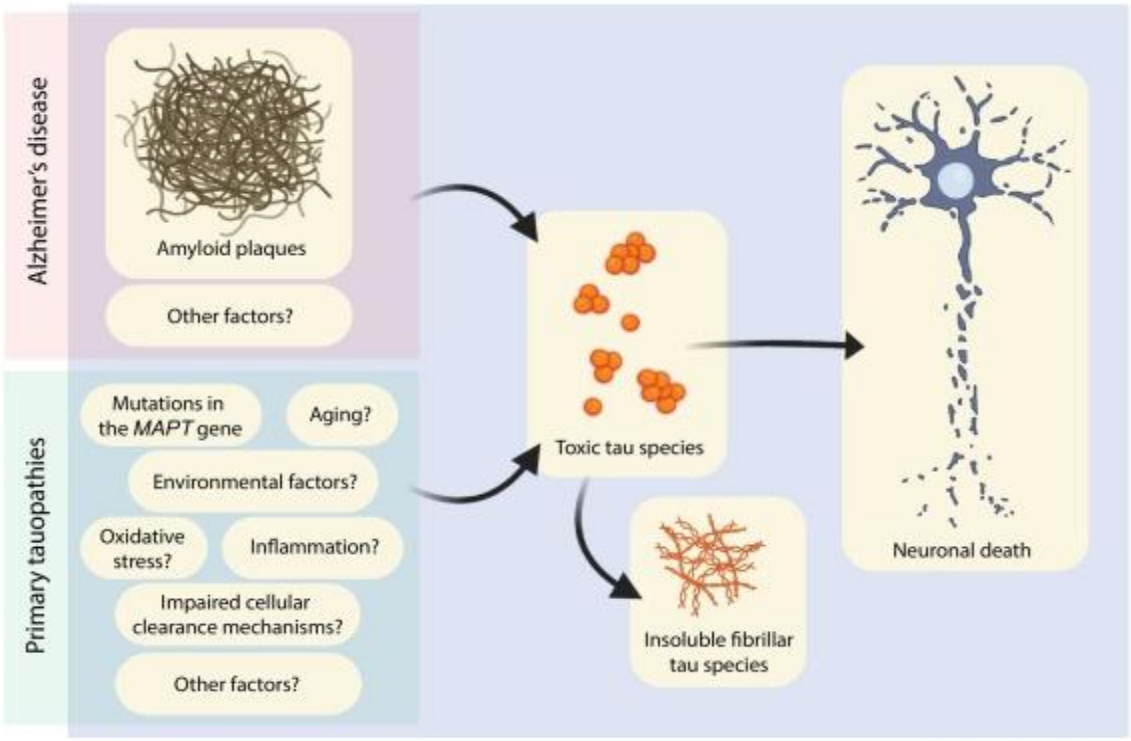

Figure 1. Characteristic lesions of Alzheimer's disease

3. Plant-Derived Bioactive Compounds in Alzheimer's Disease

According to the 10th edition of the French Pharmacopoeia, medicinal plants are defined as plant-derived substances of which at least one part exhibits therapeutic properties. These plants may also serve nutritional, culinary, or hygienic purposes. A plant is considered medicinal when one of its organs (e.g., leaves, bark, or roots) produces a therapeutic effect when used at an appropriate dose and in a specific manner, owing to the presence of bioactive constituents capable of preventing, alleviating, or treating diseases [17].

Algeria is characterized by extensive forest and rangeland ecosystems that harbor a rich and largely underexplored flora. This diversity is closely linked to the Mediterranean region, recognized as a global biodiversity hotspot [18]. In North Africa, many spontaneous plant species exhibit remarkable resistance

and adaptation to harsh environmental conditions, such as drought and salinity. These species constitute an important reservoir of genetic resources with applications in animal husbandry, nutrition, aromatherapy, and traditional medicine, in addition to their forage value. It is estimated that approximately 3,000 plant species exist in the region, of which nearly 15% are endemic [19].

Modern phytotherapy, also referred to as rational or medical phytotherapy, is grounded in scientific advances aimed at identifying and characterizing bioactive compounds in medicinal plants. This approach relies on advanced extraction techniques and the rigorous validation of biological activities through biochemical and pharmacological studies. These investigations are increasingly supported by computational tools and complemented by clinical trials, thereby enhancing the reliability and applicability of plant-based therapies [19].

One of the major advantages of phytotherapy lies in the generally high tolerability of medicinal plants when used appropriately, taking into account indications, contraindications, and potential interactions. This favorable safety profile reduces the risk of adverse effects, negative feedback mechanisms, and dependency commonly associated with synthetic drugs. Despite significant progress in modern medicine and synthetic drug development, there has been a renewed and growing interest in plant-based therapies. According to the World Health Organization, more than 80% of the global population relies on traditional pharmacopoeias for primary healthcare needs [20].

4. Classification of Natural Metabolites with Anti-Alzheimer Activity

4.1. Polyphenols

Numerous polyphenolic compounds have been identified in thousands of plant species. These compounds can be classified into different groups based on the number of phenolic rings they contain and the structural elements linking these rings. Accordingly, they are divided into several categories, including phenolic acids, flavonoids, stilbenes, and lignans. Flavonoids themselves can be further subdivided into six subclasses according to their cyclic structure: flavonols, flavones, isoflavones, flavanones, anthocyanidins, and flavanols (catechins and proanthocyanidins) [21].

Polyphenols have attracted increasing attention in the context of Alzheimer's disease (AD) due to their wide range of biological activities. They act at multiple levels: scavenging free radicals responsible for oxidative stress, interacting with transition metals that catalyze harmful reactions, and modulating the activity of numerous enzymes involved in neurodegenerative processes. In addition, they influence intracellular signaling pathways and gene expression, thereby contributing to the regulation of essential cellular functions [22].

Through their antioxidant properties, these compounds help protect cells against oxidative damage, a key factor in aging and neurodegenerative diseases. Their anti-inflammatory effects also contribute to reducing chronic inflammatory responses, which are often implicated in the progression of AD. Since oxidative stress and inflammation are central mechanisms in the aging process, polyphenols are considered potentially protective agents [21].

Moreover, polyphenols—particularly dietary lignans—play an important role in modulating the gut–brain axis. They are metabolized by the intestinal microbiota into bioactive compounds with neuroprotective properties, such as enterolactone and enterodiol. These metabolites are of therapeutic interest in neurodegenerative diseases, especially Alzheimer's and Parkinson's diseases, notably due to their ability to inhibit acetylcholinesterase and reduce advanced glycation processes [23].

Furthermore, their ability to cross the blood–brain barrier enhances their protective effects within the central nervous system. The combination of these compounds with innovative delivery systems, such as nanoparticles, is considered a promising strategy for the treatment of neurological disorders [24].

In addition, their beneficial effects are not limited to the nervous system. Polyphenols have been associated with the prevention and management of various conditions, including obesity, diabetes, osteoporosis, liver and kidney disorders, and cardiovascular diseases [25,26].

4.2. Alkaloids

Natural alkaloids represent an important class of bioactive compounds exhibiting inhibitory activity against acetylcholinesterase (AChE), an enzyme involved in the degradation of acetylcholine and in the pathophysiology of Alzheimer's disease. Several studies have demonstrated that many alkaloid molecules possess significant anticholinesterase activity. Their effectiveness is attributed to their chemical structure, particularly their positive charge at physiological pH, as well as their good bioavailability, which facilitates efficient interaction with the enzyme's active site and prolongs their in vivo activity. These characteristics make natural alkaloids a promising source of neuroactive compounds that may contribute to the development of new therapeutic strategies against neurodegenerative diseases [22,27].

Consequently, a number of plants used in traditional medicine systems as memory enhancers have been evaluated for their anticholinesterase activity. In particular, species belonging to the Amaryllidaceae, Apiaceae, Asteraceae, Fabaceae, and Fumariaceae families have shown significant potential (Table 1) [28].

Table 1. Alkaloid biomolecules with acetylcholinesterase inhibitory activity

Compound Name	**Class**	**Source**	**Botanical Family**
Assoanine	Steroidal alkaloid	Narcissus assoanus	Amaryllidaceae
Buxamine B	Steroidal alkaloid	Buxus hyrcana, Buxus papillosa	Buxaceae
Coronaridine	Indole alkaloid	Tabernaemontana australis	Apocynaceae
Corynoline	Isoquinoline alkaloid	Corydalis incisa	Papaveraceae
N,N-dimethyl buxapapine	Steroidal alkaloid	Buxus papillosa	Buxaceae
Epinorgalantamine	Steroidal alkaloid	Narcissus confusus, N. perezchiscanoi, N. leonensis, N. legionensis, Narcissus poeticus	Amaryllidaceae
Galantamine	Steroidal alkaloid	Galanthus nivalis, Narcissus confusus, Lycorus radiata	Amaryllidaceae
(-)-Huperzine A	Quinolizidine alkaloid	Huperzia serrata, Huperzia dalhousieana	Lycopodiaceae
11-Hydroxygalantamine	Steroidal alkaloid	Narcissus poeticus	Amaryllidaceae
Oxoassoanine	Steroidal alkaloid	Narcissus assoanus	Amaryllidaceae
Palmatine	Isoquinoline alkaloid	Corydalis speciosa	Papaveraceae
Protopine	Isoquinoline alkaloid	Corydalis speciosa	Papaveraceae
Physostigmine	Indole alkaloid	Physostigma venenosum	Leguminosae
Rupicoline	Indole alkaloid	Tabernaemontana australis	Apocynaceae
Sanguinine	Steroidal alkaloid	Eucharis grandiflora	Amaryllidaceae
Sarsalignone	Steroidal alkaloid	Sarcococca saligna	Buxaceae
α-Solanine	Glycoalkaloid	Solanum tuberosum	Solanaceae
Vaganine	Steroidal alkaloid	Sarcococca saligna	Buxaceae

Voacangine	Indole alkaloid	Tabernaemontana australis	Apocynaceae
Voacangine hydroxyindolenine	Indole alkaloid	Tabernaemontana australis	Apocynaceae

Acetylcholinesterase (AChE) has an active site located at the bottom of a narrow gorge, organized around a catalytic triad (Ser203, His447, and Glu334). This site comprises several functional sub-regions: an anionic subsite involved in recognizing the positive charge of acetylcholine, a hydrophobic acyl pocket that stabilizes the substrate, and an oxyanion hole essential for catalyzing hydrolysis (Figure 2). In addition, a peripheral anionic site facilitates the initial interaction with bulky substrates and guides their access to the catalytic site [29].

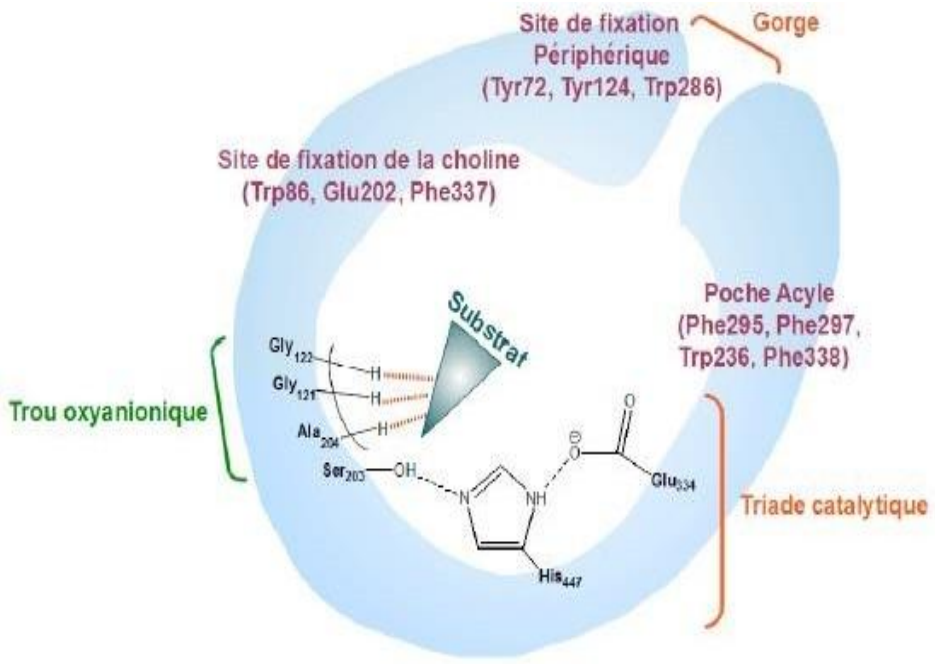

Figure 2. Schematic representation of the active site of AChE

Acetylcholinesterase (AChE) inhibitors act through two main mechanisms: reversible inhibition, generally non-covalent, which temporarily blocks the enzyme, and irreversible inhibition, often observed with certain organophosphates, involving a covalent bond with the serine residue at the active site. In the latter case, the enzyme undergoes phosphorylation, leading to prolonged or even permanent inactivation following an "aging" process that prevents reactivation. Thus, the effectiveness of inhibitors depends on their binding mode and their interactions with the different functional regions of the enzyme [30].

4.3. Terpenoids

Several natural terpenoids derived from medicinal plants and various plant sources have been investigated for their potential in the management of Alzheimer's disease. These compounds primarily target key mechanisms involved in neurodegeneration, including β-amyloid accumulation, oxidative stress, neuroinflammation, and cholinergic neurotransmission dysfunction. The most extensively studied terpenoids have demonstrated promising neuroprotective activities, particularly in in vitro and in vivo models [31].

Table 3. Terpenoid biomolecules with anti-Alzheimer activity

Terpenoid	**Main effects in Alzheimer's disease**
Ginsenosides	Improvement of cognitive functions, reduction of β-amyloid toxicity, neuroprotection via cholinergic modulation and anti-apoptotic effects
Ginkgolides	Neuroprotective and anti-inflammatory effects, improvement of cerebral circulation, platelet-activating factor (PAF) antagonism
Cannabinoids	Reduction of neuroinflammation and oxidative stress, modulation of synaptic transmission
Ursolic acid	Antioxidant and anti-inflammatory properties, protection against β-amyloid toxicity
Oleanolic acid	Antioxidant activity and reduction of amyloid-related neurotoxicity
Cryptotanshinone	Regulation of neuronal survival pathways, reduction of inflammation and oxidative stress
Tenuifolin	Memory enhancement, cholinergic and anti-amnesic effects
Iridoid glycosides (Cornus officinalis)	Neuroprotection and improvement of cognitive performance in animal models

4.4. Other Metabolites

4.4.1. Fatty Acids

Omega-3 polyunsaturated fatty acids, particularly docosahexaenoic acid (DHA), are associated with a protective effect against Alzheimer's disease, as an adequate status of these lipids is linked to improved cognitive performance and a slower rate of brain decline in the elderly. Conversely, their deficiency is correlated with the exacerbation of neurodegenerative processes, including increased cellular stress and neuronal vulnerability. Experimental studies have shown that DHA supplementation can reduce β-amyloid accumulation, limit neuroinflammation, and attenuate alterations in Tau protein. These effects are mediated through neuroprotective mechanisms involving neuronal survival, regulation of apoptosis, and modulation of brain membrane composition [32,33,34].

4.4.2. Vitamins and Minerals

Alzheimer's disease is an irreversible neurodegenerative disorder for which therapeutic options remain limited. This has intensified interest in the role of nutrition, particularly micronutrients such as vitamins and minerals, which are essential for proper brain function due to their involvement in metabolism, neurotransmission, immune response, and antioxidant defense. B vitamins contribute to energy metabolism, vitamin C acts as an antioxidant by neutralizing free radicals, and minerals play key roles in enzymatic reactions and oxidative balance. Several studies have indicated that imbalances in these micronutrients in Alzheimer's patients may promote oxidative stress, chronic inflammation, excessive glial activation, and amyloid peptide formation, all of which are involved in neurodegeneration. Therefore, maintaining an adequate micronutrient status may help to partially limit disease progression [35].

5. Innovative Approaches for the Discovery of Bioactive Biomolecules

In recent years, modern approaches in biomolecular research have experienced significant advancement through the integration of advanced analytical technologies and computational tools. Among these, metabolomics has emerged as a key strategy for biomarker identification, enabling the comprehensive analysis of metabolites within a biological system. This approach, based on techniques such as mass

spectrometry and nuclear magnetic resonance, facilitates the detection of metabolic signatures associated with specific physiological or pathological states [36].

Furthermore, in silico screening represents a major breakthrough in the discovery of bioactive biomolecules. Molecular docking allows the prediction of interactions between ligands and biological targets, thereby contributing to the selection of promising candidates prior to experimental validation. The integration of artificial intelligence, particularly through tools such as AlphaFold, has significantly improved the accuracy of structural and functional predictions of biomolecules [37,38].

In addition, integrated multi-omics approaches combining genomics, transcriptomics, proteomics, and metabolomics provide a holistic view of biological systems. These strategies enable the linkage of genetic information to observed phenotypes, thereby facilitating the understanding of metabolic pathways and the mechanisms of action of biomolecules [39,40]. Consequently, the integration of these approaches represents a key driver in accelerating the discovery and valorization of natural biomolecules.

6. Conclusion

Alzheimer's disease remains a complex and multifactorial neurodegenerative disorder for which current treatments are limited in efficacy and often associated with undesirable side effects. In this context, natural bioactive compounds derived from medicinal plants and dietary sources represent a promising alternative due to their structural diversity, biological activities, and generally favorable safety profiles. Polyphenols, alkaloids, terpenoids, as well as essential nutrients such as fatty acids, vitamins, and minerals, have demonstrated significant neuroprotective potential by targeting multiple pathological pathways involved in AD, including oxidative stress, neuroinflammation, β-amyloid aggregation, and cholinergic dysfunction.

Furthermore, the integration of advanced analytical and computational approaches, such as metabolomics, molecular docking, artificial intelligence, and multi-omics strategies, has significantly enhanced the identification, characterization, and optimization of these bioactive compounds. These interdisciplinary approaches provide a more comprehensive understanding of disease mechanisms and facilitate the development of innovative therapeutic solutions.

Nevertheless, important limitations must be acknowledged. Most of the evidence reviewed here originates from in vitro assays, animal models, or in silico predictions, and the translation of these findings into clinically meaningful outcomes remains largely unproven. Many natural metabolites, particularly polyphenols, suffer from poor aqueous solubility, low intestinal absorption, extensive first-pass metabolism, and limited capacity to cross the blood–brain barrier, which considerably restricts their bioavailability and central nervous system exposure at physiologically relevant concentrations. Standardization of plant extracts, batch-to-batch variability, and the lack of consensus on effective and safe dosing further complicate their clinical development. In addition, robust, adequately powered, and long-term randomized controlled trials in human populations are still scarce, and the heterogeneity of study designs makes cross-comparison difficult. Compared with previous reviews on natural products and Alzheimer's disease, the present work distinguishes itself by jointly addressing classical neuroprotective biomolecules and emerging computational and multi-omics discovery pipelines within a single integrative framework, thereby highlighting concrete avenues, such as encapsulation and delivery-system optimization, to bridge the gap between preclinical promise and clinical translation.

However, despite encouraging preclinical findings, further clinical studies are required to validate the efficacy, safety, and bioavailability of these compounds in humans. Future research should focus on optimizing delivery systems, improving pharmacokinetic properties, and exploring synergistic effects between natural compounds and conventional therapies. Overall, the convergence of natural product research and modern technological approaches offers a promising pathway toward the development of more effective, safer, and targeted treatments for Alzheimer's disease.

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