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Comparing the efficacy of food and pharmaceutical bioactive compounds in the management of Alzheimer's disease

[1]Jacqueline McCarthy, [2]Mkrtich Avagyan, and [3]Danik Martirosyan

[1]Boston University, Boston, MA 02215, USA; [2]AltMed, Medical Center for Rehabilitation, Preventive and Traditional Medicine, Yerevan, 0015, Armenia; [4]Functional Food Institute, San Diego, CA, 92116, USA

***Corresponding Authors:** Danik Martirosyan, Functional Food Institute, San Diego, CA, 92116, USA

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ABSTRACT

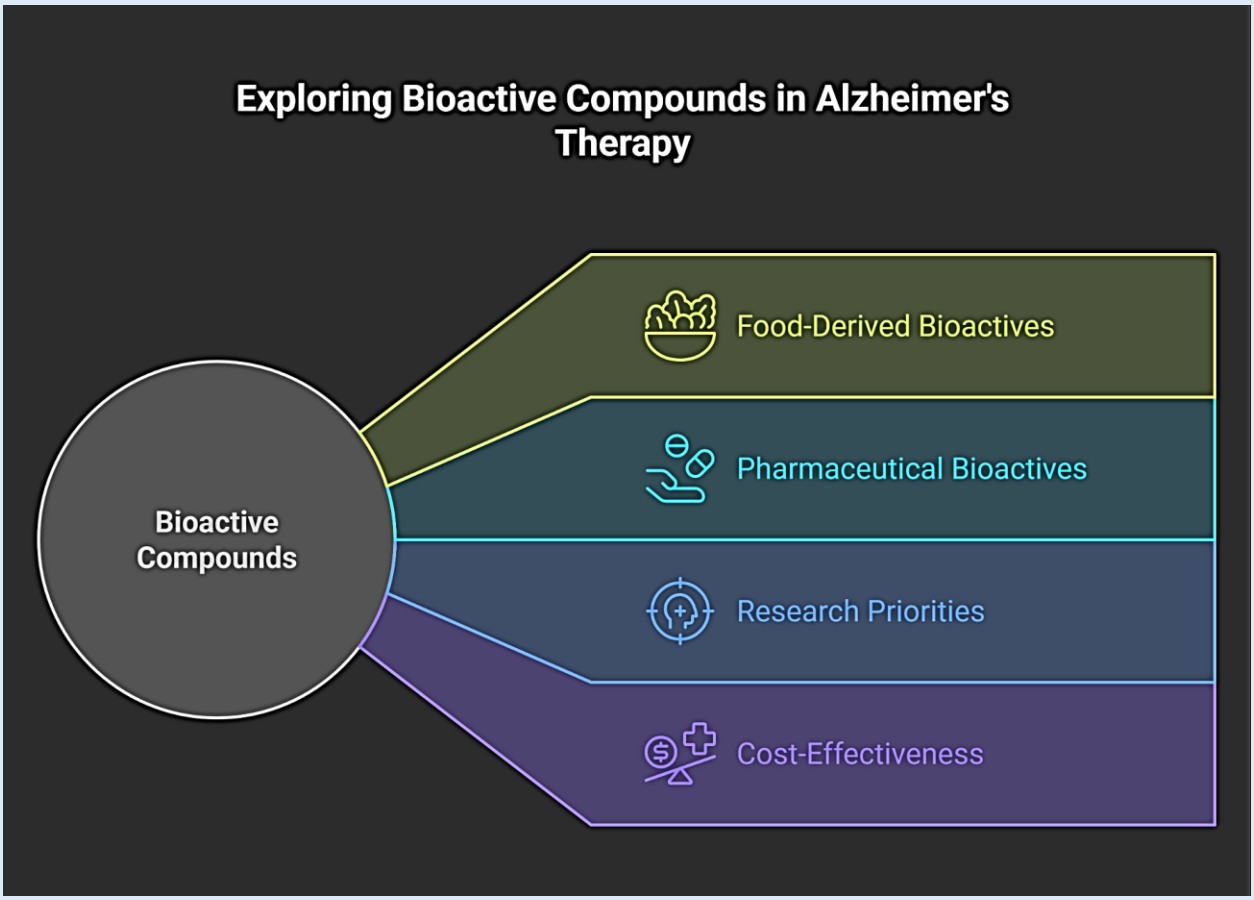
Alzheimer's disease (AD) is a progressive neurodegenerative condition and a growing global health burden, especially among aging populations. Despite ongoing therapeutic advancements, current pharmaceutical treatments remain limited in their ability to prevent, halt, or reverse disease progression. Bioactive compounds, derived from both food and pharmaceutical sources, are emerging as promising agents for AD intervention due to their diverse biological activities and mechanisms of action.

This review critically synthesizes current evidence on the therapeutic potential of bioactive compounds for AD, focusing on comparing pharmaceutical agents and food-derived compounds. Pharmaceutical bioactives often provide targeted symptom relief but are associated with limited disease-modifying effects and potential adverse reactions. Conversely, food-derived bioactive compounds demonstrate growing promise in promoting long-term neuroprotection and prevention, supported by favorable safety profiles and multi-targeted actions.

By directly contrasting these two categories, this review highlights the unique therapeutic potential of dietary bioactives and underscores the need for a paradigm shift in Alzheimer's research, from symptom management to long-term prevention strategies. This comparative analysis emphasizes the importance of shifting research priorities from short-term symptom management to long-term prevention strategies. It advocates for a more integrative approach that includes dietary bioactives as part of comprehensive AD care.

Novelty: This review uniquely highlights a critical comparative analysis between food and pharmaceutical bioactive compounds in AD therapy. It advocates for a strategic re-evaluation of research priorities from solely symptom alleviation to long-term disease prevention, thereby illuminating the undervalued role of dietary bioactives.

Keywords: Alzheimer's disease, bioactive compounds, food-derived bioactives, pharmaceutical interventions, neuroprotection, functional food, Pharmaceutical Bioactive Compounds



Graphical Abstract: Comparing the efficacy of food and pharmaceutical bioactive compounds in the management of Alzheimer's Disease.

INTRODUCTION

Alzheimer's disease (AD) is a progressive brain disorder that affects an individual's memory, thinking, and behavior [1]. It is the most common form of dementia and affects roughly ~11% of Americans aged 65 and older. However, the exact number of afflicted individuals increases significantly with age, as over one-third of individuals aged 85 and older have Alzheimer's disease [2]. The disease's progression towards cerebral atrophy and loss of brain volume causes debilitating issues with short-term episodic memory, language, and coordination. Patients commonly experience confusion, aggression, and depression as the illness progresses, and are fallible to dangerous behaviors such as wandering due to a loss of spatial awareness, leading to patients potentially getting into unsafe situations. Patients become increasingly disabled and reliant on others, typically family, to care for their hygiene and other basic needs. Eventually, the disease results in significant cellular mortality and, oftentimes, the death of the patient [3]. Given the devastating nature of the disorder and the projection that nearly 1 in 9 Americans will develop Alzheimer's disease at one point in their lives [2], finding a reliable method of preventing or treating

Alzheimer's disease is one of the highest priorities in clinical research.

One therapeutic mechanism for treating Alzheimer's disease is found in bioactive compounds, which are naturally occurring essential and non-essential compounds that have an effect on the human body [4]. Bioactive compounds are present in both food and pharmaceutical products and can have a multitude of unique mechanisms. in the body. Through exploring bioactive compounds as therapeutic agents, researchers can find a cost-effective way to treat many kinds of diseases, including Alzheimer's disease.

The purpose of this study is to conduct a thorough literature review of current available research to gain an enhanced understanding of the efficacy of food and pharmaceutical based bioactive compounds in regard to treating or preventing Alzheimer's disease.

Research Strategy: A comprehensive, electronic literature review was conducted to understand the comparative efficacy of food- and pharmaceutical-based bioactive compounds. Searches were performed on online databases such as PubMed and the Functional Food Center's journal database.

Keywords utilized during the search include "Alzheimer's disease", "bioactive compounds", "curcumin", "omega-3 fatty acids", "donepezil", "memantine", and more.

The chosen articles include in-vivo studies, clinical trials, meta-analyses, and animal models, which illustrates the full extent of known research on both food and pharmaceutical bioactive compounds in regards to the treatment and prevention of Alzheimer's disease.

Molecular Mechanisms of Alzheimer's Disease: Alzheimer's disease (AD) is a progressive neurodegenerative disorder driven by core molecular pathologies. A central mechanism involves the extracellular accumulation of amyloid-beta (Aβ) peptides, forming plaques. This occurs due to an imbalance in Aβ production from amyloid precursor protein (APP) and its clearance, with soluble Aβ oligomers being particularly neurotoxic and disrupting synaptic function [5-7].

Concurrently, intracellular hyperphosphorylation of tau protein leads to its detachment from microtubules and aggregation into neurofibrillary tangles (NFTs) [8,9]. This tau pathology disrupts neuronal transport, impairs synaptic integrity, and contributes to neuronal demise.

Neuroinflammation, primarily mediated by chronically activated microglia and astrocytes, plays a critical role in AD progression [10,11]. This sustained glial activation releases pro-inflammatory mediators, exacerbating both amyloid and tau pathologies and contributing to neuronal damage.

The interplay between these mechanisms, along with synaptic dysfunction and loss which strongly correlate with cognitive decline, underlies the disease [7,12]. Genetic factors, notably the Apolipoprotein E epsilon 4 (*APOE4*) allele, significantly influence AD risk by affecting Aβ clearance, promoting its aggregation, and modulating neuroinflammation [13-14]. Understanding these interconnected molecular pathways is crucial for developing effective therapeutic strategies.

Functional Food Perspectives in Alzheimer's Disease Management: The role of diet and specific functional foods is gaining increasing recognition as a complementary strategy in the prevention and management of Alzheimer's disease (AD), particularly by influencing its complex molecular mechanisms. Functional foods, defined as those containing biologically active compounds that provide documented health benefits beyond basic nutrition, offer a promising avenue for neuroprotection [15].

Many functional food ingredients exhibit potent antioxidant and anti-inflammatory properties, directly counteracting the oxidative stress and chronic neuroinflammation characteristic of AD [16-18]. For instance, polyphenols found in various plant-based

foods, including those in green tea extracts, grapes, and certain spices, are known for their ability to scavenge free radicals and modulate inflammatory pathways [16-17,19]. Specific compounds like quercetin, a flavonoid present in onions, have shown potential in improving cognitive function and reducing decline by exhibiting antioxidant and anti-inflammatory effects [20].

Beyond broad antioxidant and anti-inflammatory actions, certain functional food components may directly influence core AD pathologies. Research indicates that bioactive compounds can support neuronal health by affecting membrane integrity and neurotrophin signaling, such as brain-derived neurotrophic factor (BDNF) [21-22]. While clinical trials on direct AD management are still evolving, preliminary findings suggest benefits from compounds like those in fenugreek seeds (for neuroprotection and synaptic preservation) and black bone chicken (for neuroprotective and anti-inflammatory benefits) [15,18].

The impact of functional foods is often attributed to their ability to provide a synergistic blend of bioactive compounds, rather than single isolated nutrients. This holistic approach can target multiple pathways implicated in AD, including modulation of gut microbiota, which is increasingly linked to brain homeostasis and neuroinflammation via the gut-brain axis [19,23]. While ongoing research continues to elucidate the precise dosages and long-term efficacy, integrating functional foods rich in diverse bioactive compounds represents a promising, accessible, and low-risk approach to potentially support cognitive health and delay AD progression [15,20].

Food Bioactive Compounds: Food-derived bioactive compounds have played a significant role in prevention of Alzheimer's disease, such as omega-3 fatty acids, flavonoids, and probiotics [24].

To understand how these compounds work, it's crucial to examine their effect on a key aspect of AD pathophysiology: oxidative stress. Alzheimer's disease's pathophysiology is rooted in an intraneuronal accumulation of soluble amyloid β (Aβ) oligomers in the central nervous system (CNS), alongside the buildup of tau protein bundles within nerve cells. In the brain of an Alzheimer's disease patient, the cells undergo high levels of oxidative stress due to amyloid plaques being the focus of cellular and molecular oxidation, which promotes the production of more Aβ peptides, resulting in a positive feedback loop. The rise in oxidants leads to increased misfolding and conformational changes in proteins, as they are notoriously major targets of reactive oxygen species (ROS). The oxidative modifications leads to the emergence of cross-linked protein aggregates, which are heavily linked to the pathogenesis of Alzheimer's disease [25].

Flavonoids and polyphenols, found most commonly in apples and citrus fruits [25], have been noted to possess neuroprotective properties that can slow the progression of the disease or prevent it entirely. Their antioxidant characteristics are due to their ability to directly scavenge free radicals or indirectly enhance the body's own antioxidant defenses, such as activating the Nrf2 transcription factor pathway [26]. All forms of flavonoids possess the same core structure, which consists of two benzene rings (A and B) joined by a pyranosic ring (C). The many hydroxyl groups present on the B ring allow flavonoids to donate electrons and hydrogen atoms to radical species to reduce their reactivity [25]. By doing so, the flavonoid radical is significantly more stable, resulting in a notable reduction in oxidative stress and therefore an impeded progression of Alzheimer's disease.

Natural phenolic compounds such as curcumin, found in turmeric or *Curcuma longa*, also possess anti-inflammatory and antioxidant characteristics that make it useful in preventing and treating Alzheimer's disease. Curcumin inhibits the formation of Aβ oligomers, alongside Aβ and tau aggregation [27]. In addition to

reducing the accumulation of neurotoxic protein aggregates, curcumin has been shown to modulate oxidative stress pathways and decrease neuroinflammation, both of which are central to the progression of neurodegeneration. Its ability to cross the blood-brain barrier and influence multiple molecular targets further underscores its potential as a multifaceted therapeutic agent in Alzheimer's research [28]. However, curcumin's clinical utility is limited by its low bioavailability, prompting researchers to explore nanoparticle formulations and adjuvants such as piperine to enhance its systemic absorption [29].

Resveratrol, a polyphenolic compound found in grapes and red wine, has also demonstrated promise in AD models. It activates sirtuin-1 (SIRT1), which plays a role in neuronal protection, mitochondrial function, and synaptic plasticity [30]. Resveratrol has also been shown to inhibit amyloid-beta-induced toxicity and reduce neuroinflammation in vitro and in vivo [31]. However, similar to curcumin, resveratrol faces pharmacokinetic challenges due to rapid metabolism and poor central nervous system penetration, limiting its therapeutic efficacy in human trials [32].

Another compound of interest is EGCG, the main catechin in green tea. EGCG has been shown to inhibit amyloid-beta fibrillization, chelate metal ions involved in oxidative stress, and modulate signaling pathways such as PI3K/Akt and MAPK [33]. Animal studies have indicated that EGCG supplementation improves cognitive performance and synaptic integrity [34]. Human trials remain limited but suggest that EGCG may have modest cognitive benefits when administered in high doses [35].

Recent research shows that omega-3 polyunsaturated fatty acids (n-3 PUFAs), particularly docosahexaenoic acid (DHA), play a vital role in supporting cognitive health and may offer protective benefits against neurodegenerative diseases such as Alzheimer's. DHA, a major structural component of neuronal membranes, contributes to maintaining synaptic function and neuronal integrity. It also possesses anti-inflammatory and neuroprotective properties that help mitigate oxidative stress and reduce the accumulation of neurotoxic proteins commonly observed in Alzheimer's pathology. Higher dietary intake and plasma levels of DHA have been associated with a decreased risk of cognitive decline and dementia. Although results vary depending on factors such as age, genetics, and disease stage, these findings support the potential of omega-3s as a valuable component in strategies aimed at preserving brain health and preventing or delaying the progression of Alzheimer's disease [36].

The potential of probiotics as a therapeutic approach for AD has also been an emerging focus in recent studies. Probiotics, beneficial live microorganisms, have been shown to exert neuroprotective effects through multiple mechanisms. These include reducing oxidative stress, modulating neuroinflammation, and improving gut-brain axis (GBA) communication. Studies in animal models of AD have demonstrated that probiotic supplementation can lead to decreased amyloid-beta (Aβ) plaque accumulation, enhanced antioxidant enzyme activity, and improved cognitive functions such as memory and learning. Furthermore, probiotics may influence the composition of gut microbiota, leading to the production of neuroactive compounds that support neuronal health. These findings suggest that incorporating probiotics into the diet could be a promising strategy for mitigating the progression of AD and enhancing cognitive function [37].

In addition to these naturally occurring compounds, vitamin D and B-complex vitamins have also been implicated in AD management. Vitamin D has neuroprotective roles through calcium homeostasis, antioxidant regulation, and modulation of immune responses [38]. B vitamins, particularly B6, B9 (folic acid), and B12, are essential in homocysteine metabolism, a process linked to cognitive decline and AD risk [39].

Several studies suggest that B vitamin supplementation can slow cognitive deterioration, especially in individuals with elevated homocysteine levels [40]. However, as with many nutraceuticals, individual responses vary, and the long-term effects require further exploration through well-powered clinical trials.

Table 1 summarizes the types of food-based bioactive compounds discussed in current literature and their corresponding beneficial and adverse effects.

Table 1. Summary of Food-Based Bioactive Compounds.

Name of Bioactive	Beneficial Effects	Adverse Effects or Drawbacks	Source
Flavonoids	Antioxidant, neuroprotective properties slow progression	No reported adverse effects, limited clinical trials	[25,26], [61-64]
Curcumin	Antioxidant, prevents accumulation of neurotoxic protein aggregates	No adverse effects, low bioavailability, limited clinical trials	[27-29], [61-64]
Resveratrol	Anti-inflammatory, neuroprotective properties, enhances mitochondrial function and synaptic plasticity	No adverse effects, low bioavailability, limited clinical trials	[30-32], [61-64]
EGCG	Inhibits amyloid-beta fibrillization and oxidants; improved cognitive performance, synaptic integrity	No adverse effects, limited human clinical trials	[33-35], [61-64]
Omega-3 fatty acids	Anti-inflammatory, neuroprotective properties	No reported adverse effects, limited human clinical trials	[36], [61-64]
Probiotics	Antioxidant, anti-inflammatory, improved GBA communication	No reported adverse effects, limited human clinical trials	[37], [61-64]
Vitamin D, Vitamin B	Neuroprotective properties; calcium homeostasis, antioxidant, modulates immune responses	Individual results vary; long term effects require further investigation through clinical trials	[38-40]

As a whole, food-based bioactive compounds show significant promise for treating and preventing Alzheimer's disease and deserve increased attention from researchers.

Pharmaceutical Bioactive Compounds: The more conventional method of treating Alzheimer's is with pharmaceuticals, particularly pharmaceutically based bioactive compounds. Among the primary pharmaceutical agents utilized in treating AD are donepezil and memantine.

Donepezil is an acetylcholinesterase inhibitor, most commonly taken as a pill once per day. One of the significant changes resulting from Alzheimer's disease is a reduction in cholinergic neurons, a type of nerve cells, which use acetylcholine to signal to other cells. Donepezil prevents acetylcholine from being broken down, which improves symptoms of dementia. However, donepezil also has some mild to severe side effects, such as nausea, vomiting, and diarrhea [41].

Memantine, an N-methyl-D-aspartate (NMDA)-receptor antagonist, is another pharmaceutical utilized in treating Alzheimer's disease. In large quantities, glutamate, a primary excitatory neurotransmitter, can overstimulate the brain's neurons, leading to neuronal damage and calcium overload associated with the pathogenesis of neurodegenerative disorders. Memantine has been implicated in improving patient outcomes and providing therapeutic benefits for patients with advanced dementia. This includes decreased

deterioration, especially in comparison with placebo. Memantine also carries its share of adverse side effects, such as agitation, urinary incontinence, urinary tract infections (UTIs), insomnia, and diarrhea [42].

Beyond donepezil and memantine, other pharmacological agents have been investigated to target different aspects of Alzheimer's disease (AD) pathology. Rivastigmine and galantamine, like donepezil, are cholinesterase inhibitors that increase acetylcholine levels in the brain. Rivastigmine has a dual inhibitory action on both acetylcholinesterase and butyrylcholinesterase, potentially offering enhanced benefits in patients with mixed dementias or Parkinson's disease dementia [43]. Clinical trials have demonstrated improvements in cognitive function and daily living activities, though gastrointestinal side effects remain a limiting factor [44].

Combination therapy is another approach gaining traction. Some studies suggest that using both memantine and a cholinesterase inhibitor may offer synergistic benefits, particularly in moderate to severe stages of AD. Patients treated with both memantine and donepezil have shown slower cognitive and functional decline compared to monotherapy [45]. However, this approach is not without controversy, as not all trials have consistently replicated these benefits, and the combined side effect burden must be carefully weighed [46].

Another promising class of pharmaceutical bioactive compounds used in Alzheimer's disease (AD) management is huperzine A, a naturally derived alkaloid that is pharmaceutically synthesized and formulated. It acts as a reversible acetylcholinesterase inhibitor and exhibits neuroprotective effects. Multiple randomized controlled trials have demonstrated improvements in memory function, cognitive performance, and activities of daily living in AD patients treated with huperzine A, especially in Chinese populations [47]. Its favorable pharmacokinetics, including high oral bioavailability and good blood-brain barrier penetration, make it a viable candidate for further development [48].

Tramiprosate, a GABA analog, has attracted attention due to its ability to inhibit amyloid-beta aggregation. Although the large Alphase trial did not meet its primary endpoints in the general AD population, post-hoc analyses revealed cognitive benefits in homozygous APOE ε4 carriers, suggesting that genetic profiling may guide its targeted use [49]. A new prodrug formulation, ALZ-801, aims to improve tramiprosate's bioavailability and gastrointestinal tolerability. Preliminary results have indicated potential efficacy in reducing amyloid accumulation and slowing disease progression in genetically defined subgroups [50].

Bexarotene, a retinoid X receptor (RXR) agonist approved for cutaneous T-cell lymphoma, has shown potential in preclinical AD models. It promotes expression of ApoE and enhances clearance of amyloid-beta peptides by microglia. Early mouse studies indicated dramatic reductions in amyloid plaques and cognitive improvement, though these findings have not been consistently replicated in humans [51]. Clinical trials have yielded mixed results and reported adverse effects such as hyperlipidemia and hepatotoxicity, limiting its clinical utility [52].

Another investigational drug, latrepirdine (Dimebon), originally used as an antihistamine in Russia, showed early promise for treating AD due to its multifaceted mechanisms, including mitochondrial stabilization and neuroprotection. A Phase II trial demonstrated cognitive and behavioral improvement, but these effects were not reproduced in larger Phase III studies, leading to its eventual discontinuation for AD indications [53]. The latrepirdine case underscores the challenge of translating early positive signals into long-term clinical success in neurodegenerative disorders.

Tideglusib, a small molecule inhibitor of glycogen synthase kinase-3β (GSK-3β), has been proposed as a therapeutic agent for AD due to its role in reducing tau hyperphosphorylation and promoting neuronal survival. While early trials hinted at improved cognitive outcomes and reductions in tau pathology, subsequent studies showed no significant changes in primary endpoints,

though the compound remains under investigation for other neurodegenerative conditions [54].

More recently, sodium oligomannate (GV-971) has emerged as a novel agent with regulatory approval in China. Although derived from marine algae, it is synthesized and standardized pharmaceutically. GV-971 is thought to act by modulating gut microbiota and reducing peripheral and central inflammation, ultimately impacting amyloid deposition. A global Phase III trial is ongoing to validate its efficacy beyond initial regional studies [55].

Finally, 5-HT6 receptor antagonists, including PF-05212377 (SAM-760) and idalopirdine, have been studied for their capacity to enhance cholinergic and glutamatergic transmission indirectly. While the rationale is strong, especially given serotonin's role in modulating cognition, multiple Phase II and III trials failed to demonstrate significant cognitive benefits. Both compounds were eventually dropped from development, reflecting the complexity of targeting serotonergic systems in AD [56,57].

Table 2 summarizes the pharmaceutical bioactive compounds discussed in this section, alongside relevant beneficial and adverse effects.

Table 2. Summary of Pharmaceutical-Based Bioactive Compounds.

Name of Bioactive	Beneficial Effects	Adverse Effects	Source
Donepezil	Improves symptoms of dementia	Nausea, vomiting, diarrhea, brachycardia; inconsistent efficacy; cognitive decline when discontinuing medication	[41], [58-60]
Memantine	Decreased rate of deterioration	Agitation, urinary incontinence, UTIs, insomnia, diarrhea, brachycardia; inconsistent efficacy; cognitive decline when discontinuing medication	[42], [58-60]
Rivastigmine, galantamine	Cognitive benefits	Gastrointestinal side effects	[43,44]
Huperzine A	Neuroprotective effects; improves memory function and cognitive performance	None reported	[47,48]
Tramiprosate	Cognitive benefits	Primary Alphase trial did not meet primary endpoints; gastrointestinal side effects	[49]
ALZ-801	Improves on tramiprosate's bioavailability and gastrointestinal side effects; helps slow disease progression	Prodrug still in development	[50]
Bexarotene	Reductions in amyloid plaques and cognitive improvement in mice trials	Hyperlipidemia and hepatotoxicity; clinical trials have yielded mixed results; limited clinical utility	[51,52]
Latrepirdine	Mitochondrial stabilization; neuroprotective properties; cognitive and behavioral improvement	Beneficial effects from Phase II study were not reproduced in larger Phase III studies	[53]
Tideglusib	Promotes neuronal survival; reduces tau hyperphosphorylation	Subsequent studies showed no significant changes in primary endpoints	[54]
GV-971 (sodium oligomannate)	Anti-inflammatory; modulates gut microbiota; impacts amyloid deposition	Still undergoing clinical trials	[55]
SAM-760, idalopirdine	Indirectly enhances cholinergic and glutamatergic transmission	Did not show significant cognitive benefits	[56,57]

In summary, pharmaceutical bioactive compounds such as donepezil and memantine remain central to the clinical management of Alzheimer's disease, offering symptomatic relief despite notable side effects. Emerging and experimental agents—including huperzine A, tramiprosate, bexarotene, latrepirdine, tideglusib, sodium oligomannate, and 5-HT6 receptor antagonists—reflect growing efforts to address the complex pathophysiology of Alzheimer's through diverse mechanisms. While many have shown early promise, few have demonstrated consistent clinical success, underscoring the ongoing need for rigorous research, targeted therapies, and personalized treatment strategies in the fight against this debilitating neurodegenerative disease.

DISCUSSION

The therapeutic landscape for Alzheimer's disease (AD) is evolving, with both food-based and pharmaceutical bioactive compounds offering distinct yet complementary avenues for intervention. While each category demonstrates measurable benefits, their mechanisms, accessibility, side effect profiles, and long-term implications differ significantly.

Pharmaceutical interventions such as donepezil and memantine are well-characterized through rigorous clinical trials and remain the gold standard in current AD management [58-59]. These drugs target specific neural pathways, namely cholinergic and glutamatergic signaling, to alleviate cognitive symptoms. However, they provide limited long-term disease modification and are often associated with adverse effects, ranging from gastrointestinal issues to neuropsychiatric symptoms. For instance, bradycardia has been reported more frequently with donepezil (10%) compared to memantine (7%), highlighting the need for careful monitoring during treatment [59]. Furthermore, their efficacy often reaches a plateau, and discontinuation often results in rapid cognitive decline [60].

In contrast, food-based bioactive compounds such as flavonoids, curcumin, and omega-3 fatty acids operate on a broader physiological scale. These compounds target multiple pathological hallmarks of AD, such as oxidative stress, neuroinflammation, and protein misfolding, often with fewer side effects [61,62]. While their pleiotropic nature is a strength, it also presents challenges in establishing standardized dosing and efficacy due to variability in absorption, metabolism, and bioavailability [63]. Moreover, clinical trials on food bioactives often face limitations such as small sample sizes, short durations, and inconsistencies in formulation [64].

Accessibility is another differentiating factor. Food-derived compounds can be integrated into daily diets, potentially offering a preventative approach that is both affordable and scalable [65]. In contrast, pharmaceuticals require diagnosis, prescription, and ongoing monitoring, limiting their utility as early-intervention or preventative tools.

Importantly, current evidence suggests that while pharmaceuticals offer faster symptom relief, food-based compounds may offer longer-term neuroprotection and disease modification when introduced early, especially in preclinical or prodromal stages [28]. However, conclusive head-to-head comparisons are scarce, and future research must focus on controlled trials that directly assess their relative efficacy, optimal timing of intervention, and potential combined effects.

Figure 1 illustrates the timeline of Alzheimer's disease progression, and the points where either food or pharmaceutical bioactive compounds are most effective at preventing or managing the disease.

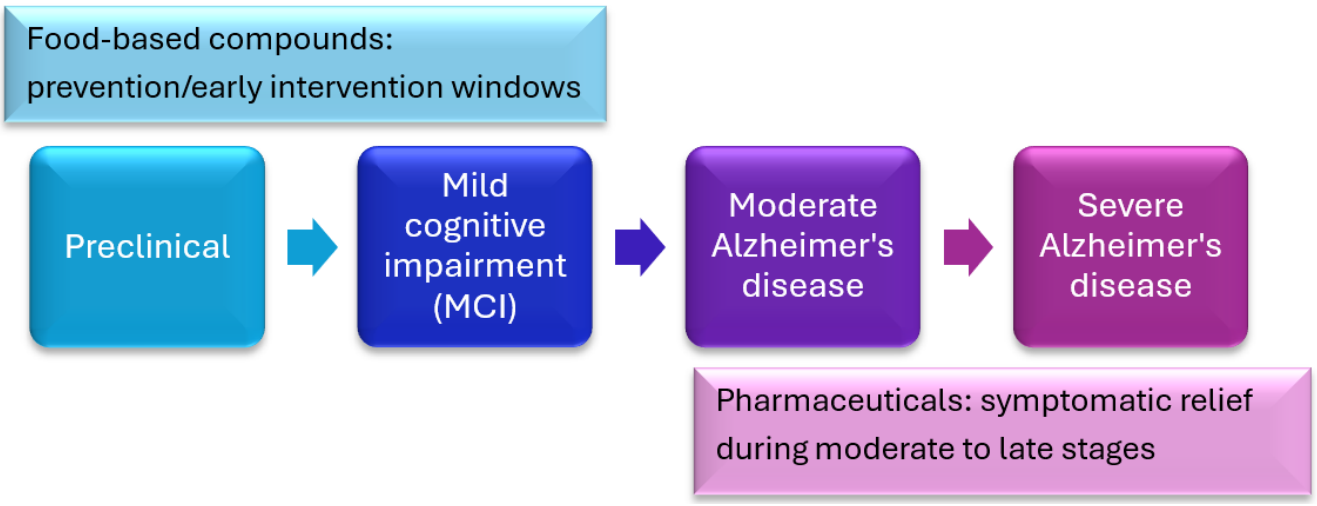


Figure 1. Stages of Alzheimer's Disease and Points of Bioactive Intervention.

In summary, pharmaceutical bioactive compounds offer targeted, immediate relief for Alzheimer's symptoms, but may fall short in altering disease trajectory. Food-derived compounds, although less potent in acute symptom management, hold promise for long-term neuroprotection with fewer side effects. A strategic shift in research emphasis—from symptom alleviation to disease prevention—may elevate the role of dietary bioactives in future Alzheimer's care.

Scientific Innovation: Multitargeting the Pathophysiology of Alzheimer's Disease: Scientific innovation in Alzheimer's disease (AD) treatment is moving towards a multifaceted approach, leveraging both established pharmaceutical mechanisms and the pleiotropic effects of food-derived bioactive compounds. A key area of innovation lies in understanding and exploiting the diverse mechanisms by which these compounds interact with the complex pathophysiology of AD. For instance, food-derived bioactive compounds like flavonoids and curcumin are recognized for their antioxidant and anti-inflammatory properties, directly targeting oxidative stress and neuroinflammation, which are central to AD progression. Their ability to scavenge free radicals and modulate signaling pathways like Nrf2 represents a significant scientific advancement in mitigating cellular damage. Furthermore, the capacity of compounds like curcumin and omega-3 fatty acids (DHA) to inhibit the formation of neurotoxic protein aggregates (Aβ oligomers and tau bundles) and maintain neuronal integrity showcases an innovative shift towards preventing the foundational molecular events of the disease. The emerging understanding of the gut-brain axis and the neuroprotective potential of probiotics, which influence gut microbiota composition and reduce oxidative stress and neuroinflammation, further exemplifies a broader, systemic approach to AD research. This contrasts with the more targeted, symptom-management approach of traditional pharmaceuticals, highlighting a paradigm shift towards upstream intervention and disease modification.

Practical Implications: Integrating Prevention and Treatment Strategies: The practical implications of research into bioactive compounds for Alzheimer's disease are profound, suggesting a future where preventative and therapeutic strategies are more integrated and accessible. The recognition of food-derived bioactive compounds, such as omega-3 fatty acids, flavonoids, and curcumin, as potential neuroprotective agents opens avenues for dietary interventions that could delay or prevent AD onset, particularly in at-risk populations. This offers a cost-effective and scalable approach to public health, moving

beyond the traditional model of relying solely on prescription medications after disease manifestation. While pharmaceutical agents like donepezil and memantine remain crucial for managing symptomatic AD, their side effect profiles and limited long-term disease modification underscore the need for complementary strategies. The development of functional foods or supplements enriched with these bioactive compounds could empower individuals to proactively manage their brain health. Practically, this implies a greater emphasis on nutritional guidance in clinical settings, potentially leading to personalized dietary recommendations as part of AD prevention and management plans. However, challenges remain in standardizing dosages and ensuring bioavailability of food bioactives, necessitating further research to translate scientific findings into reliable clinical guidelines and products.

Challenges in Managing Alzheimer's Disease: A Practitioner's Perspective: From the front lines of clinical practice, managing Alzheimer's Disease (AD) presents a multifaceted array of challenges that extend far beyond simply identifying cognitive decline. Early diagnosis, while increasingly emphasized, remains a significant hurdle. Patients often present with subtle, non-specific symptoms in the initial stages, which can be easily dismissed as normal aging, stress, or other comorbidities [66]. This diagnostic ambiguity is compounded by the lack of readily available, definitive, and affordable diagnostic tools for early, pre-symptomatic detection in routine practice [67,68]. While advanced neuroimaging and cerebrospinal fluid biomarkers exist, their accessibility and cost can be prohibitive, particularly in primary care settings [67].

Beyond diagnosis, the progressive nature of AD introduces a continuous and evolving set of difficulties. We witness patients gradually lose their ability to perform daily activities, communicate effectively, and even recognize loved ones. This decline necessitates ongoing adaptation of care plans, often requiring difficult conversations with both patients and their families about diminishing independence, safety concerns (such as driving), and future care needs [69]. Behavioral and psychological symptoms, including agitation, delusions, and depression, are common and can be particularly distressing for caregivers, often requiring careful medication management and non-pharmacological interventions [70-71].

Furthermore, the current therapeutic landscape, while showing promising advancements, is still limited. Existing medications primarily offer symptomatic relief or slow the rate of cognitive decline, rather than providing a cure or reversing the disease process [72-73]. The introduction of newer disease-modifying therapies, while hopeful, comes with its own complexities, including the need for early diagnosis, careful patient selection, and monitoring for potential side effects [72,74].

Finally, the immense emotional, physical, and financial burden on caregivers is a constant concern [75-76]. As practitioners, we often find ourselves serving not just the patient, but also their family, providing guidance, resources, and emotional support as they navigate the challenging journey of caring for a loved one with AD [76]. The fragmented nature of healthcare systems, coupled with shortages of specialists (like geriatricians and neurologists) and limited community resources, further complicates our ability to provide truly comprehensive and coordinated care, creating a continuous demand for more integrated, patient- and family-centered approaches [75].

CONCLUSION

The current landscape of Alzheimer's disease research highlights a promising future where both pharmaceutical and food-derived bioactive compounds contribute to a comprehensive strategy for prevention and treatment. While conventional pharmaceuticals offer targeted relief for cognitive symptoms, food-based bioactives present a

compelling avenue for long-term neuroprotection by addressing multiple pathological hallmarks of AD with potentially fewer side effects. The scientific innovations in understanding the pleiotropic mechanisms of compounds like flavonoids, curcumin, and omega-3 fatty acids, alongside the emerging role of probiotics and the gut-brain axis, underscore a shift towards upstream intervention and disease modification. Practically, this suggests a move towards integrated approaches that combine symptomatic management with preventative dietary strategies, emphasizing accessibility and early intervention. Future research must focus on rigorous comparative studies, optimal dosing, and bioavailability to fully realize the potential of these compounds and translate scientific promise into effective clinical and public health interventions for Alzheimer's disease.

List of Abbreviations: AD: Alzheimer's disease, Aβ: amyloid-beta, APP: amyloid precursor protein, NFT: neurofibrillary tangle, APOE4: Apolipoprotein E epsilon 4, BDNF: brain-derived neurotrophic factor, CNS: central nervous system, ROS: reactive oxygen species, SIRT1: sirtuin-1, n-3 PUFAS: omega-3 polyunsaturated fatty acids, DHA: docosahexaenoic acid, GBA: gut-brain axis, NMDA: N-methyl-D-aspartate, GABA: gamma-aminobutyric acid, RXR: retinoid X receptor, GSK-3β: glycogen synthase kinase-3β, GV-971: sodium oligomannate.

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