

# Therapeutical potential of nutraceuticals in the prevention and management of Alzheimer's disease

## Abstract

Alzheimer's disease (AD) is a long-term brain neurodegenerative condition. Approximately 55 million individuals worldwide currently suffer from dementia. The WHO projects that the number of people with AD will reach over 78 million globally by 2030 and almost 139 million by 2050. In recent years, nutraceuticals – supplements to contemporary medicine that provide health benefits – have become more well-known. Using nutraceuticals could potentially reduce complete dependence on prescription drugs while minimizing side effects, due to their unique chemical properties. Often, nutraceuticals have special chemical properties that aren't seen in medications. Treatments for AD primarily target  $\beta$ -amyloid ( $A\beta$ ). However, due to its poor permeability, medications that target  $A\beta$  are difficult to utilize. Other drugs, such as NMDA-receptor antagonists and cholinesterase inhibitors, when combined, only temporarily relieve the symptoms of AD. Hence, nutraceuticals are being researched to potentially slow down the progression of dementia and in the management of AD. Reported clinical trial failures of AD drugs in literature, mostly in phase 2 & 3 trials, are mainly due to a lack of evidence of effectiveness as they failed to cross the blood-brain barrier (BBB). The use of new therapies, such as specific nutraceuticals, and their latest delivery approaches facilitates the entry of active ingredients into the BBB such as nanoencapsulation and liposomal based delivery systems. These new therapies work on a novel method of delivery of nutraceuticals and have shown their effectiveness in clinical studies in the management of AD. This study examines how medicinal nutraceuticals may be useful in the management of AD.

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## Introduction

Alzheimer's disease (AD) is a progressive neurological condition affecting memory, language, and other cognitive functions; it is also the most common cause of dementia [1,2,3]. The drugs currently in use for AD are primarily symptomatic, including one glutamate receptor antagonist (memantine) and four acetylcholinesterase inhibitors (tacrine, donepezil, rivastigmine, and galantamine). These drugs offer modest benefits but are not curative. Consequently, research is focused on developing new treatment strategies for AD, aiming to alter the disease's biology or enhance cognitive performance through alternative means [4]. Among these approaches are medical foods, nutraceuticals, and dietary modifications [5].

The field of human health and nutrition is experiencing a renaissance, driven by the discovery and investigation of the disease-fighting potential of various phytochemicals found in both food and non-food plants. This has led to numerous opportunities for creating innovative food products. A new term – “nutraceuticals” – has emerged in this context [6].

The term “nutraceutical” refers to a food product that provides health and medical benefits, including the prevention and treatment of disease. It combines “nutrition” and “pharmaceutical” to describe products ranging from processed foods like cereals, soups, and drinks to genetically engineered foods, herbal products, isolated nutrients, and personalized diets [7,8].

Recent research has shown that lifestyle modification techniques, including dietary changes and nutritional supplements, can be beneficial in preventing cognitive decline, AD, and vascular conditions. Nutrients, dietary supplements, natural dietary sources and supplement mixes, social and mental engagement and physical activity have all been identified as potential strategies in the prevention of AD [9].

Collectively, these dietary strategies and supplements are referred to as nutraceuticals.

Despite their potential advantages, nutraceuticals face significant challenges due to poor brain permeability, metabolism, and bioavailability [10,11]. Unfortunately, there has been limited scientific research on nutraceuticals and herbal medicines, despite their long history of traditional use and apparent safety and effectiveness.

Herbal medical practices suggest various plants and their components to improve cognitive function and alleviate other AD symptoms, such as depression, memory loss, and poor cognition [12].

## Nutraceutical concepts

Dr Stephen L De Felice first defined the term nutraceutical. According to Dr De Felice, nutraceuticals are products derived or purified from food, typically presented in pharmaceutical forms not commonly associated with food, which have been shown to provide physiological benefits or protection against chronic diseases [13,12]. Recent research indicates that lifestyle modification strategies; such as dietary components, natural nourishment and supplement formulations, mental and social activities, physical conditioning, and nutrients, can positively impact the development of cognitive decline, Alzheimer's disease (AD), and vascular dementia [10]. In pharmaceutical development, clinical data from animal studies and results are required to confirm the effects of drugs. Historically, the concept that certain foods could prevent specific diseases was not widely accepted in nutrition. However, recent scientific validation of food composition as a factor in lifestyle-related illnesses has elevated this topic to a significant social issue. From the consumer's perspective, nutraceuticals and functional foods (foods containing biologically active components, such as vitamins, minerals, fibre or antioxidants to help

improve health, prevent disease, or enhance well-being) offer several potential advantages [14]. They can:

1. Enhance the healthfulness of our diets.
2. Potentially extend lifespan.
3. Assist in the prevention of specific medical conditions.
4. Provide psychological benefits through self-care.
5. Be perceived as more “natural” and less likely to cause adverse side effects compared to conventional medicine.
6. Cater to populations with special dietary needs (e.g. nutrient-dense foods for the elderly) [7,14]

### Enhancing AD treatments using novel techniques

The development of effective medications to treat AD has advanced very slowly over the past 20 years. A major obstacle to this effort has been the inability of many medications to cross the blood-brain barrier (BBB) [15]. This barrier is necessary to shield the brain from dangerous compounds but also keeps many potentially helpful medications from reaching their intended target. A further consequence of the BBB is lack of proof about the efficacy of certain medications during clinical trials, which has resulted in several failures and setbacks in the treatment of AD. Approximately 100% of large-molecule medicines and over 98% of small-molecule drugs cannot penetrate the BBB. The majority of AD drug candidates do not cross the BBB so a deliberate effort must be made in future AD drug development to include BBB studies early in the central nervous system (CNS) drug discovery process [16]. AD drugs target various sites in the brain to manage symptoms, including the Cholinergic System, Glutamatergic System, Amyloid-beta (Aβ) Plaques, Tau Proteins, Neuroinflammation, Oxidative stress, etc.

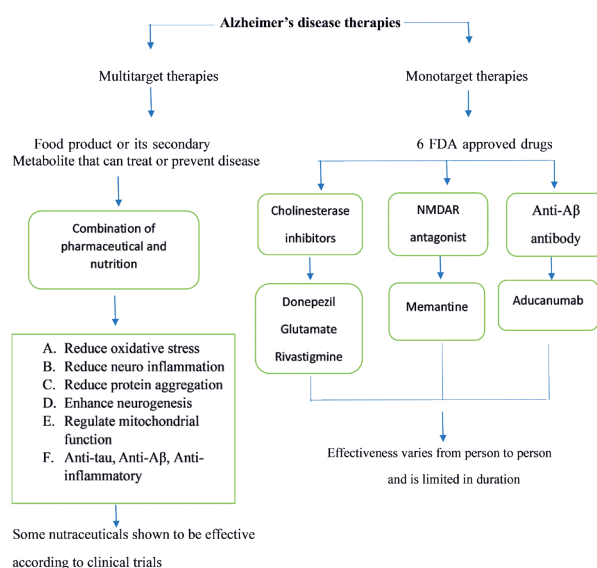
New drugs that target these numerous sites in AD, when combined with BBB drug delivery

technology, may provide new and efficacious treatments for this condition. Some of these novel therapies may involve the use of various forms of nutraceuticals (resveratrol, curcumin, ginkgo biloba) and different nanoencapsulation methods, which have been proven to show effectiveness in preventing AD in recent clinical trials. Drugs can be delivered to the brain via nanosized carriers; examples include Nano emulsions, solid lipid-based carriers, and liquid and solid lipid-based carriers.

These formulations can target essential brain transport systems and encapsulate active compounds, facilitating medication uptake across the BBB [17].

## Classification of nutraceuticals

Nutraceuticals are employed in non-specific biological therapies to enhance health, promote well-being, and prevent minor symptoms of chronic illnesses. They are widely recognized for their neuroprotective properties, which contribute to brain health and the prevention of neurodegenerative diseases such as AD and dementia, as illustrated in Fig. 1 [10,18,19].

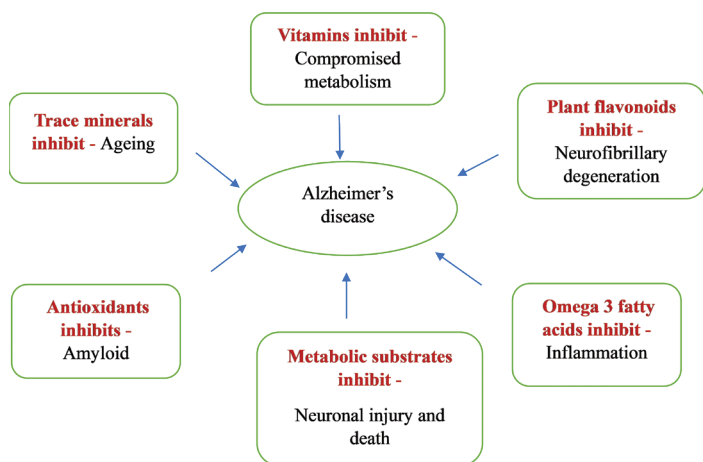


**Figure 1** The working mechanism of nutraceuticals and conventional drugs in treating AD [20]

## Various categories of nutraceuticals used in the management of AD

### (A) Nutrients

Nutrients, such as vitamins, minerals, amino acids and fatty acids, are essential to metabolic pathways and play a beneficial role in treating neurological conditions like AD [7]. Delaying neuronal death is crucial for managing AD and developing effective treatment plans. Macronutrients, including vitamins E, C, and the B family, and micronutrients like DHA, support neuronal adaptation to aging. These nutrients are widely accepted by the general public due to their affordability, safety, accessibility and essential role in life. The vitamin B family, including pyridoxine, cobalamin, and folate is particularly significant in treating neurological conditions. Folate is vital for DNA methylation, but its levels can be reduced by malabsorption and poor diets. Vitamin B12, essential for homocysteine metabolism, lowers the risk of cardiovascular disease and enhances cognitive performance. Conversely, an inadequate diet can indirectly affect gene expression regulation and disease progression [21].



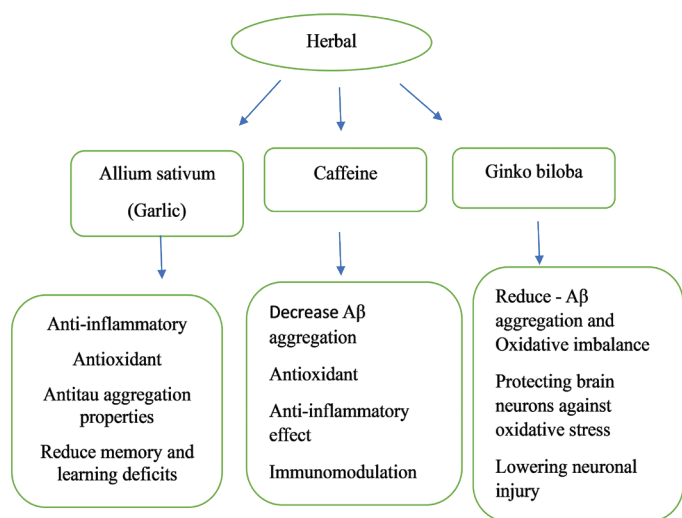
**Figure 2** The working mechanism of nutrients (vitamins, minerals) on AD

### (B) Herbals

Herbals have been used since the dawn of human civilization and offer a vast array of remedies for both acute and chronic illnesses. Over thousands of years, knowledge of herbal remedies has expanded, providing numerous efficient approaches to modern healthcare. With the aid of herbals, nutraceuticals have potential for promoting health and aiding in the management of some chronic diseases.

1. **Ginkgo biloba:** *G. biloba* is a well-researched herb that may help individuals with mild cognitive impairment or AD by enhancing memory, cognition, and overall brain health [22,23]. Studies have demonstrated the antioxidant and free-radical scavenging properties of ginkgo extracts, which contain 24% ginkgo-flavone glycosides and 6% terpenoids [24]. The flavonoids in ginkgo are particularly beneficial in treating neurodegenerative diseases, especially AD [25]. Benefits of ginkgo include reducing the effects of sub-chronic cold stress on receptor desensitization, protecting brain neurons against oxidative stress, lowering neuronal injury following electroconvulsive shock or ischemia, and reducing oedema and bromethalin-induced cerebral lipid peroxidation. Further research is required to fully understand the components of ginkgo extract and its potential advantages for individuals with AD [26–30].
2. **Garlic (*Allium sativum*):** Allicin, an organosulfur component found in garlic extracts, has antioxidant properties and protects against neurotoxicity, particularly amyloid-beta-induced neurotoxicity [31,32]. Studies suggest garlic extracts may be beneficial in treating AD. However, higher allium consumption has not always been linked to reduced cognitive decline; in some cases, it has been observed to impair cognitive function and flexibility [10,33]. The bioactive molecule S-allyl cysteine (SAC) in aged garlic has an-

ti-inflammatory, antioxidant, anti-A $\beta$ , and antitau aggregation properties. Specifically, SAC prevents tau from aggregating by reducing the activity of glycogen synthase kinase 3 beta (GSK-3 $\beta$ ). It can also inhibit caspase 3 and prevent endoplasmic reticulum stress (ER stress) [20]. The mechanism of action of garlic in managing AD is illustrated in Fig. 3.



**Figure 3** The working mechanism of herbal medicine in managing AD [20]

3. Isoflavones in soybeans: Rich in phytoestrogens, particularly isoflavones, soybeans have been investigated as potential replacements for estrogenic nutraceuticals in the treatment of AD. Isoflavones mimic the effects of oestrogen in the brain, enhancing cognitive performance by agonistically affecting oestrogen receptors [34,35]. Long-term soybean supplementation has been shown to improve cognitive function, reduce reactive chemicals related to thio-barbituric acid, and increase levels of plasma glutathione peroxidase, indicating antioxidant properties [36,37].
4. Caffeine: In animal models of AD, caffeine, a xanthine alkaloid, has been shown to reduce the generation of amyloid-beta and possess antioxidative qualities [38,39]. It acts as a non-selective antagonist of adenosine

receptors, similar to adenosine. Caffeine consumption is linked to enhanced cognitive function, alertness, normal brain function, and a slower rate of cognitive decline. Case-control research has found that high caffeine levels are associated with a decreased risk of dementia progression in individuals with mild cognitive impairment [40,41]. However, the potential of caffeine to prevent neurodegenerative diseases like dementia and AD remains constrained by inconsistent evidence, necessitating further research [10].

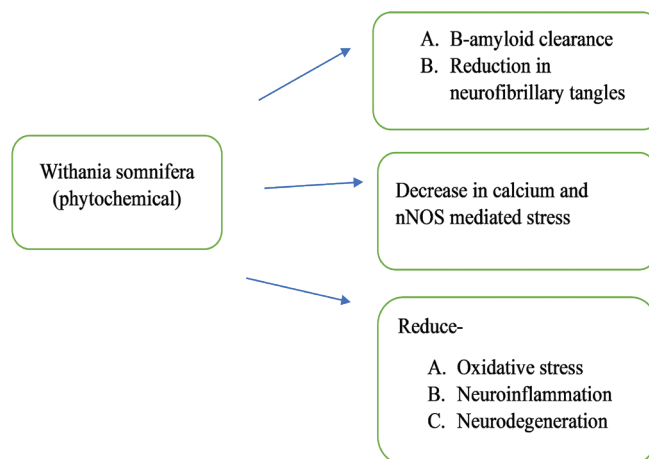
### (C) Phytochemicals

Phytochemicals are categorized based on their chemical composition; they are derivatives of phenolic compounds which are neither minerals nor vitamins.

1. Flavanols: Flavanols, such as quercetin, are secondary metabolites found in chocolate, cocoa, grapes, green tea, and black tea. These compounds have been shown to have positive physiological, biochemical, and antioxidant effects, particularly on vascular function. Flavanols can scavenge free-radicals, reduce inflammation and protect cells from damage. Regular consumption of fruits high in flavanols can lower the incidence of AD and increase levels of kaempferol and myricetin, which help prevent cognitive decline [42,43]. Therefore, consuming fruit high in flavonoids may positively affect cognitive function [44].
2. Polyphenols (non-Flavonoids): Resveratrol and curcumin are prominent polyphenolic compounds derived from plants. Turmeric naturally contains curcuminoids (curcumin and desmethoxycurcumin), while red grapes are rich in resveratrol. These compounds have demonstrated potential as anti-AD substances in various studies [45,46]. Research has shown that non-flavonoid polyphenols exhibit positive outcomes *in vivo* models and cell cultures studying neu-

rotoxicity, the longevity-linked gene sirtuin 1, and their antioxidant qualities [45,47].

3. **Curcumin:** Curcumin, the active component of turmeric, has been shown to improve cognitive abilities in individuals with AD. It exhibits neuroprotective, lipophilic, antioxidant, and anti-inflammatory properties, reducing beta-amyloid, oxidative stress, free-radicals and abnormal inflammatory responses [48,49]. Due to its unique chemical structure, curcumin has garnered attention for its potential to target antioxidant and inflammatory pathways while reducing amyloid aggregation, a key indicator of AD [10,49,50].
4. **Resveratrol:** Resveratrol, a phyto-phenol found in red grapes, exhibits strong antioxidant properties. Recent research indicates that resveratrol can prevent ischemic damage to neurons in the brain and spinal cord and penetrates the central nervous system (CNS) quickly after peripheral injection [51]. Resveratrol has antidepressant qualities, potentially explained by its ability to enhance 5-HT activity. It increases serotonin levels in the hippocampus while inhibiting the re-uptake of noradrenaline and 5-HT [52,53]. Additionally, resveratrol can reduce inflammation and prevent neuron death, protecting cultured neurons from oxidative stress-induced death caused by nitric oxide [54,55,56]. It has also been shown to protect dopaminergic neurons from oxidative and metabolic damage in midbrain slice cultures [51].
5. **Ashwagandha:** Ashwagandha (*Withania somnifera*) is a herb that supports memory and cognition. Beta-amyloid plaques, which accumulate in the brains of individuals with various neurodegenerative diseases, are thought to be harmful to neurons. Studies suggest that *Withania somnifera* can significantly alter basic brain functions and may be used therapeutically to prevent and treat central nervous system (CNS) disorders [51,57,58].



**Figure 4** The working mechanism of *Withania somnifera* (phytochemical) on AD

#### (D) Dietary supplements:

Dietary supplements are products taken orally that contain dietary components used to enhance food intake. According to the Dietary Supplement Health and Education Act (DSHEA, 1994) a dietary supplement is defined as “a product that contains one or more of the dietary ingredients, such as a vitamin, mineral, herb, or other botanical, and amino acid (protein), and also includes any possible component of the diet as well as concentrates, constituents, extracts, or metabolites of these compounds” [59]. Examples of dietary supplements include glucosamine/chondroitin for arthritis, black cohosh for menopausal symptoms and ginkgo biloba for memory loss. They also serve specific functions, such as sports nutrition, weight loss supplements and meal replacements [60]. Supplements contain various nutritional components, including organ tissues, gland extracts, vitamins, minerals, botanicals, herbs, amino acids, enzymes, and other nutrients [61,62]. They are available in multiple dosage forms, including tablets, capsules, liquids, powders, extracts, and concentrates [21].

#### (E) Prebiotics and probiotics

Recent research has explored the role of the microbiome in neurodegenerative illnesses, highlighting the importance of the gut-brain

axis in developing these disorders. Prebiotics and probiotics are essential for maintaining a healthy microbiota and should be considered among the novel compounds that could be used in AD prevention [63,64].

**1. Prebiotics:** The term “prebiotic” refers to a non-digestible food component that enhances the host’s health by promoting the growth and activity of beneficial bacteria in the colon. This concept was first introduced in 1995 [65]. Prebiotics are composed of carbohydrates, such as resistant starch and  $\beta$ -glucan, resistant to digestive system secretions and enzymes [66]. Upon reaching the colon, gut microflora ferments these carbohydrates, promoting the growth of commensal strains while inhibiting harmful bacteria [67].

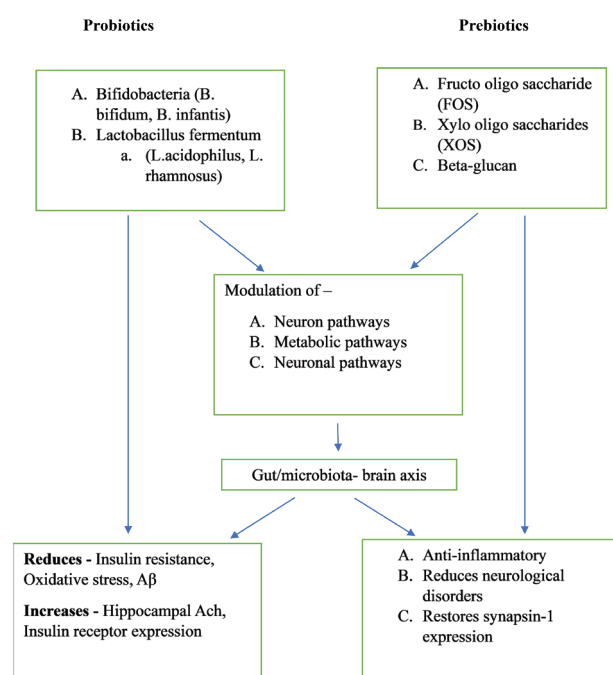
**1.1. Fructo oligosaccharide (FOS):** FOS is the most researched prebiotic. It is a fructose-based short-chain oligosaccharide joined by  $\beta$  (2->1) glycosidic linkages [68]. This substance, produced when inulin breaks down, is present in many fruits and vegetables. It serves as a substrate for the growth of Lactobacillus and Bifidobacterium in the microflora [69].

**1.2. Xylo oligosaccharides (XOS):** XOS are another well-researched prebiotic with encouraging benefits. XOS, the most prevalent biopolymer in the plant kingdom, is produced from oligomers of Xylan [70]. Due to its accessibility and anti-inflammatory characteristics, XOS is a prime candidate for cognitive impairment testing. For instance, the cognitive function of APP/PS1 mice with hepatectomy-induced postoperative cognitive dysfunction (POCD), a common comorbidity of AD, improved when supplemented with XOS [71].

**1.3. Beta-glucan:** Beta-glucan, a linear, non-branched polysaccharide, increases viscosity and provides a good substrate for gut microorganisms [72]. High molecular weight  $\beta$ -glucan consumption enhances bifidogenic action, SCFA synthesis, and the growth of Bacteroides and Prevotella [73,74].

**2. Probiotics:** Probiotics are defined as “live microorganisms which, when administered in ade-

quate amounts, confer a health benefit on the host” [75]. Significant probiotics include Bifidobacteria (*B. bifidum*, *B. infantis*) and Lactobacilli (*Lactobacillus acidophilus*, *L. rhamnosus*). They are often referred to as “functional foods” [76]. These commensal microbes impact neurodegenerative illnesses, including AD, by altering the levels of critical regulators such as brain-derived neurotrophic factor (BDNF), GABA, dopamine (DA), and serotonin (5-HT), thereby affecting cognition and behaviour [77].



**Figure 5** Mechanism of prebiotics and probiotics in treating AD [20]

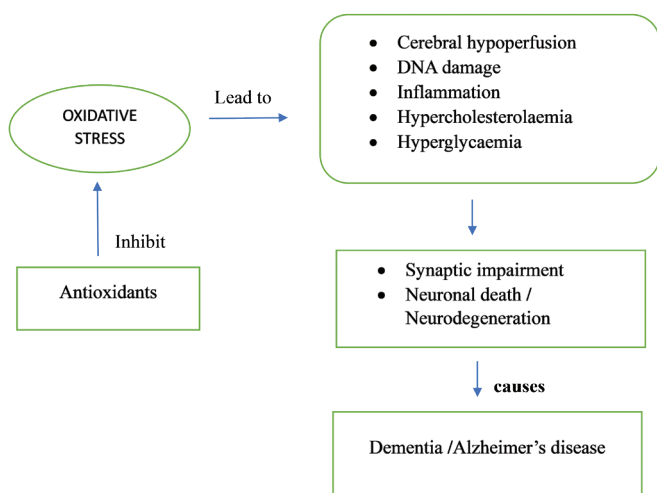
Prebiotics and probiotics have significant mechanisms in AD: As described in Fig. 5, they influence cytokines and improve insulin resistance in the CNS, exhibiting neuroprotective and anti-inflammatory properties. Prebiotics such as Beta-glucan, XOS, and FOS are particularly beneficial [20]. The mode of action of probiotics in AD includes immunological modulation, endocrine pathways, and neuronal regulation [78]. When administered in required quantities, probiotics enhance host health through anti-inflammatory, antioxidant, anti-A $\beta$ , and immunomodulatory properties, as well as insulin regulation. For ex-

ample, kefir, a probiotic, has numerous positive health effects [20].

### (F) Antioxidants

Since oxidative stress is a major component of most chronic diseases, antioxidants are crucial for the treatment of nearly every illness. Oxidative stress is a significant factor in neurodegenerative illnesses like AD [79].

1. Alpha-Lipoic Acid (ALA): ALA plays a crucial role in brain activity. Oxidative stress and energy depletion are hallmark traits of AD. ALA, a strong antioxidant, promotes glucose consumption and metabolism in the brain. The regulation of AD by ALA is illustrated in Fig 6 [80]

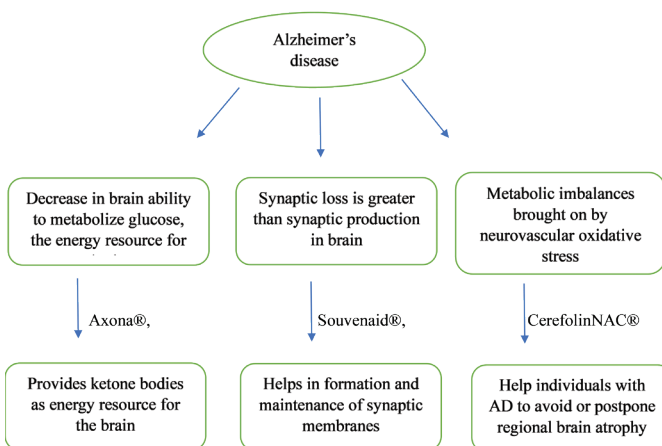


**Figure 6** The working mechanism of antioxidants in managing AD [81]

2. Phosphatidylserine: Phosphatidylserine is an interesting compound, the primary phospholipid in the brain, forming the fundamental structure of cell membranes. It is essential for biochemical signalling and cell-to-cell communication. Oral intake of phosphatidylserine enhances neuronal membranes, cell metabolism, and certain neurotransmitters such as acetylcholine, norepinephrine, serotonin, and dopamine. It also improves cellular metabolism and communication [7,82].

### (G) Medical foods

The US FDA (2013), under the Orphan Drug Act's section 5(b) (21 U.S.C. 360ee (b) (3)), defines medical food as "a food formulated to be consumed or administered enterally under the supervision of a physician and intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation" [83]. Medical foods cater to the unique nutritional requirements of individuals with diseases or metabolic disorders. Examples include Axona®, Souvenaid®, and CerefolinNAC®, marketed in the USA and Europe for their potential benefits in dementia patients. This article examines the latest scientific data supporting the use of these medical foods in treating AD and to lessen AD symptom severity [5].



**Figure 7** The working mechanism of medical foods in treating AD

1. Axona®: Axona® consists of medium-chain caprylic triglycerides. Consuming coconut or palm kernel oil in the diet is insufficient to meet the caprylic triglyceride demands of individuals with AD [84]. The rationale behind Axona® is that ketone bodies serve as an alternative energy source to compensate for reduced glucose metabolism in the brains of individuals with AD. Axona® is said to benefit the clinical dietary management of mild-to-moderate AD metabolic processes [1,85].



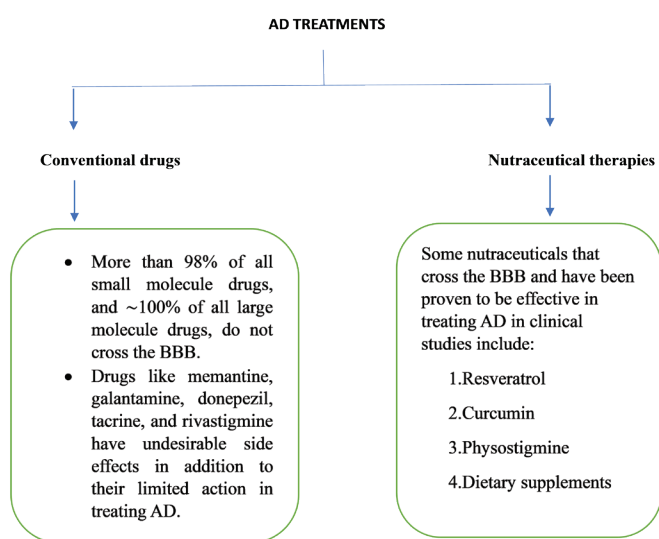
2. Souvenaid®: Souvenaid® is a dietary composition formulated to enhance synapse development. Approved for early AD treatment in several European countries and Australia, this multi-nutrient beverage contains eleven vitamins and supplements. The formulation includes supportive nutrients and phosphatide precursors meant to improve membrane and synapse function in individuals with AD. It contains higher concentrations of phospholipids, selenium, uridine monophosphate, choline, folic acid, selenium, and omega-3 fatty acids (docosahexaenoic and eicosapentaenoic acid) than is found in a typical diet [1,86,87].
3. CerefolinNAC®: CerefolinNAC® addresses metabolic imbalances caused by neurovascular oxidative stress and hyper-homocysteinaemia, associated with cognitive decline. It may help individuals with AD to avoid or delay regional brain atrophy [1,88].

Nutraceuticals	Mechanism of action	Reference
<b>Nutrients</b>		
B vitamin family: Vitamins B6, B12, B9	Vitamins B6, B9, and B12 are important in brain function, which includes respiration, vision, motor abilities, memory, emotion, and cognition. These vitamins are also beneficial for the production of many neurochemicals and for the synthesis and repair of DNA and RNA.	10
Vitamin A	Antioxidants are important for both the treatment of certain skin conditions and for growth and development.	7
Antioxidant vitamins: C	Ascorbic acid, or vitamin C, is essential for the synthesis of dopamine and noradrenaline, two neurotransmitters involved in the regulation of tyrosine metabolism. Vitamin E is also required since it functions as a strong antioxidant.	10
Antioxidant vitamins: E	Vitamin E is also required since it functions as a strong antioxidant	10
<b>Herbals</b>		
Ginkgo biloba	Ginkgo biloba improves the reduction of neuronal damage by lowering cell membrane lipid peroxidation and oedema against bromethalin-induced cerebral lipid peroxidation.	12
Garlic ( <i>Allium sativum</i> )	Allicin, an organosulfur found in <i>Allium sativum</i> , increases acetylcholine levels in the brain by inhibiting cholinesterase enzymes.	10
Isoflavones: soybeans	Isoflavones imitate the effects of oestrogen by enhancing the antioxidant properties of the brain's oestrogen receptor $\beta$ , which appears to boost cognitive performance.	10
Caffeine	A xanthine alkaloid, caffeine can decrease amyloid-beta production by quenching hydroxyl radicals.	10
<b>Phytochemicals</b>		
Flavanols: gallate, isorhamnetin, kaempferol, myricetin, epicatechin, epigallocatechin, and quercetin	Flavanols' biological components can scavenge free radicals (oxidative stress) in the blood and the gut, reduce inflammation, and shield cells from harm.	10
Non-flavonoid polyphenols: resveratrol and curcumin	Resveratrol can reduce inflammation and neuronal damage. Curcumin is an anti-inflammatory and may also support the immune system.	51
Ashwagandha	Alters basic brain functions and may be used to prevent and treat some of CNS disorders therapeutically like AD, Parkinson's, and Huntington's.	12
<b>Antioxidants</b>		
Alpha-lipoic acid	Alpha-lipoic acid's anti-inflammatory and antioxidant qualities help the CNS produce cellular energy.	10
Phosphate-lysine	Improves cellular metabolism	7
<b>Medical foods</b>		
Axona®	Neurons with impaired glucose utilization have an alternate energy source thanks to the metabolism of caprylic acid to ketone bodies.	1
Souvenaid®	Impacts on improvements in synapse formation and deficiencies in the composition and function of neuronal membranes.	1
CerefolinNAC®	Impact of hyper-homocysteinaemia on metabolic dysregulation and neuronal oxidative stress	1
<b>Prebiotics and probiotics</b>		
Prebiotics	Have anti-inflammatory and neuroprotective effects.	20
Probiotic	Anti-A $\beta$ , anti-inflammatory, antioxidant, and immunomodulatory properties	20

**Table 1** The working mechanism of different nutraceuticals on AD

## Comparison between conventional drugs and nutraceutical therapies in managing AD

Most conventional drugs that are clinically approved for the treatment of AD, such as memantine, galantamine, donepezil, tacrine and rivastigmine do not enter the brain in effective concentrations due to several factors including their inability to cross the BBB, poor solubility and hepatic breakdown. The need for new approaches in drug development to overcome these challenges may include the use of nutraceuticals, which are clinically proven to be effective in managing AD by crossing the BBB.



**Figure 8** Comparison between conventional drugs and nutraceutical therapies in managing AD [15,16,17,89]

### Nutraceuticals that cross the BBB and are proven to be effective in clinical studies

#### Resveratrol

Individuals with AD who received resveratrol treatment had decreased levels of MMP-9, a matrix metalloproteinase associated with neurodegeneration. This implies that resveratrol fortifies the CNS by lowering permeability,

which limits the brain’s accessibility to pro-inflammatory substances. Additionally, levels of beta-amyloid in the cerebrospinal fluid (CSF) declined more slowly. These results validate the possible therapeutic benefits of resveratrol. The CSF contained sizable concentrations of resveratrol and its metabolites, demonstrating the substance’s capacity to effectively pass through the BBB. The results of the two clinical trials provided credence to the idea that resveratrol could be a safe and effective therapy for AD.

#### Curcumin

Curcumin has less toxicity and a greater absorptivity to the BBB. Curcumin’s neuroprotective impact has been linked to its suppression of microglial activation. Previous studies have demonstrated the anti-inflammatory and free radical scavenging effects of curcumin. [17]

#### Dietary supplements

Various dietary supplements showed improvement in the severity of symptoms (self-reported or evaluated by doctors) in randomized controlled studies, suggesting that supplementing may be beneficial. [89]

#### Physostigmine

The most therapeutically successful carbamate type has been rivastigmine, which is currently approved for treatment in individuals with AD with mild to moderate dementia symptoms [17]

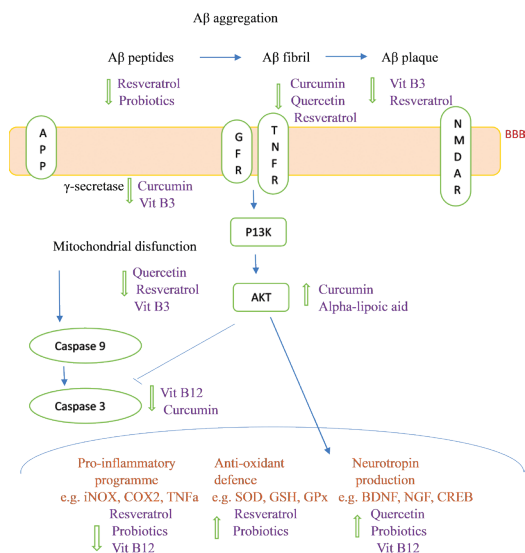
## A nutraceuticals-based approach in AD management

AD is a multifactorial disease that is influenced by a number of risk factors, one such major factor is increase in amyloid beta (Aβ) deposition, which reduces cerebral blood flow, induces neuroinflammation and oxidative

stress and may impair the BBB, all of which may accelerate the progression of AD.

Recently, various anti-A $\beta$  treatment pathways have been extended to preclinical phases of AD. The majority of drugs currently approved in the treatment of AD are only meant to address short-term symptoms. Therefore, utilizing nutraceuticals in management of AD can be an effective approach in reducing the progression of the disease.

Nutraceutical accumulation in the brain activates pathways including the PI3K/Akt signalling pathway, which stimulates the synthesis of neurotrophins. Neurotrophins are the class of growth factor, a type of proteins that promote the survival, development, and differentiation of neurons and regulate the neuron functions. The majority of nutraceuticals exhibit multimodal neuroprotective potential by exhibiting their ability to reduce proinflammatory processes and apoptosis, while also having a considerable impact on the aggregation of A $\beta$  peptides.



**Figure 9** Signalling pathways regulated by nutraceuticals that underlie certain neuroprotective mechanisms in the treatment of AD [90]. Up arrows indicate upregulation of expression and activity. Down arrows indicate a downregulation of expression and activity.

APP = Amyloid precursor protein. A $\beta$  = Amyloid beta. 1. GFR = Growth factor receptor. TNFR = Tumour necrosis factor receptor. COX-2 = Prostaglandin-endoperoxide synthase 2. TNF $\alpha$  = Tumour necrosis factor- $\alpha$ . iNOS = Inducible nitric oxide synthase. SOD = superoxide dismutase. GSH = Glutathione. GPx = Glutathione peroxidase. BDNF = Brain-derived neurotrophic factor. NGF = Nerve growth factor

## Discussion

The nutrients in a wide variety of foods, including fruits and vegetables, are well-established for their health benefits. Despite numerous studies and systematic reviews, scientific research on dietary strategies and herbal supplements for delaying or stopping the progression of neurodegenerative illnesses like AD remains limited. However, the number of studies investigating nutraceutical interventions to postpone or prevent cognitive impairment and slow the onset of AD is rapidly increasing. With the advancements in neuroscience, ongoing research aims to identify target molecules, pharmacophores, and phytochemicals to develop treatments for degenerative diseases like AD using contemporary technologies and high throughput screenings.

## Conclusion

The various nutraceuticals discussed in this review, such as the B vitamin family, carotenoids, antioxidants, such as vitamin C and E, isoflavones, flavanols, curcumin, resveratrol, garlic, ginkgo biloba, prebiotics and probiotics, and medical foods, represent significant advancements in the management of AD. Recent studies suggested that naturally occurring bioactive compounds may benefit the aging brain by improving debilitating brain pathology and enhancing cognitive function.

The difficulty of active molecules to cross the BBB is the main hurdle in drug delivery to treat AD. Novel approaches such as nano technology, mono clonal antibodies, liposome-based drug delivery, etc can facilitate the permeation of drugs and bioactive molecules through BBB. Herbal extracts with a single herb, many herbs, or a combination of herbs and minerals, may have neuroprotective effects by delaying the onset of AD symptoms.

These natural products are possible sources of bioactive substances that might be helpful in the treatment of AD. Further research is needed to validate the efficacy of bioactive compounds and innovative drug delivery technologies in the management of AD.

## Conflict of interest

The authors declare that they have no conflict of interest.

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