Review Article **Open Access**

Exploring the potential of bioactive compounds as interventions for dementia: current insights and future directions

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Submission Date: March 12th, 2024; **Acceptance Date:** May 1st, 2024; **Publication Date**: May 3rd, 2024

Please cite this article as: Nicholas-Okpara V. A. N., Adegboyega M. O., Oben J. E., Williams L., Utazi A. I., Rhema J. K., Akanno C., Ubaka A. J. Exploring the Potential of Bioactive Compounds as Interventions for Dementia: Current Insights and Future Directions. *Functional Food Science* 2024; 4(5): 166-179. DOI: https://doi.org/10.31989/ffs.v4i5.1329

ABSTRACT:

BACKGROUND: Dementia is a prevalent geriatric condition that affects a significant number of people around the world, and its prevalence is projected to reach 153 million people by 2050. It is characterized by a gradual decline in cognitive function. Despite extensive research efforts, the underlying pathology of dementia remains unclear, although multiple complex processes have been implicated. Presently, there is no definitive cure for dementia, and the discovery of pharmaceutical interventions capable of completely stopping the progress of the disease remains an ongoing pursuit. In recent years, the potential of bioactive compounds as alternative or complementary interventions for various diseases has gained substantial attention.

OBJECTIVE: This review aims to critically evaluate the current utilization of bioactive compounds as interventions for dementia in older adults living with the condition.

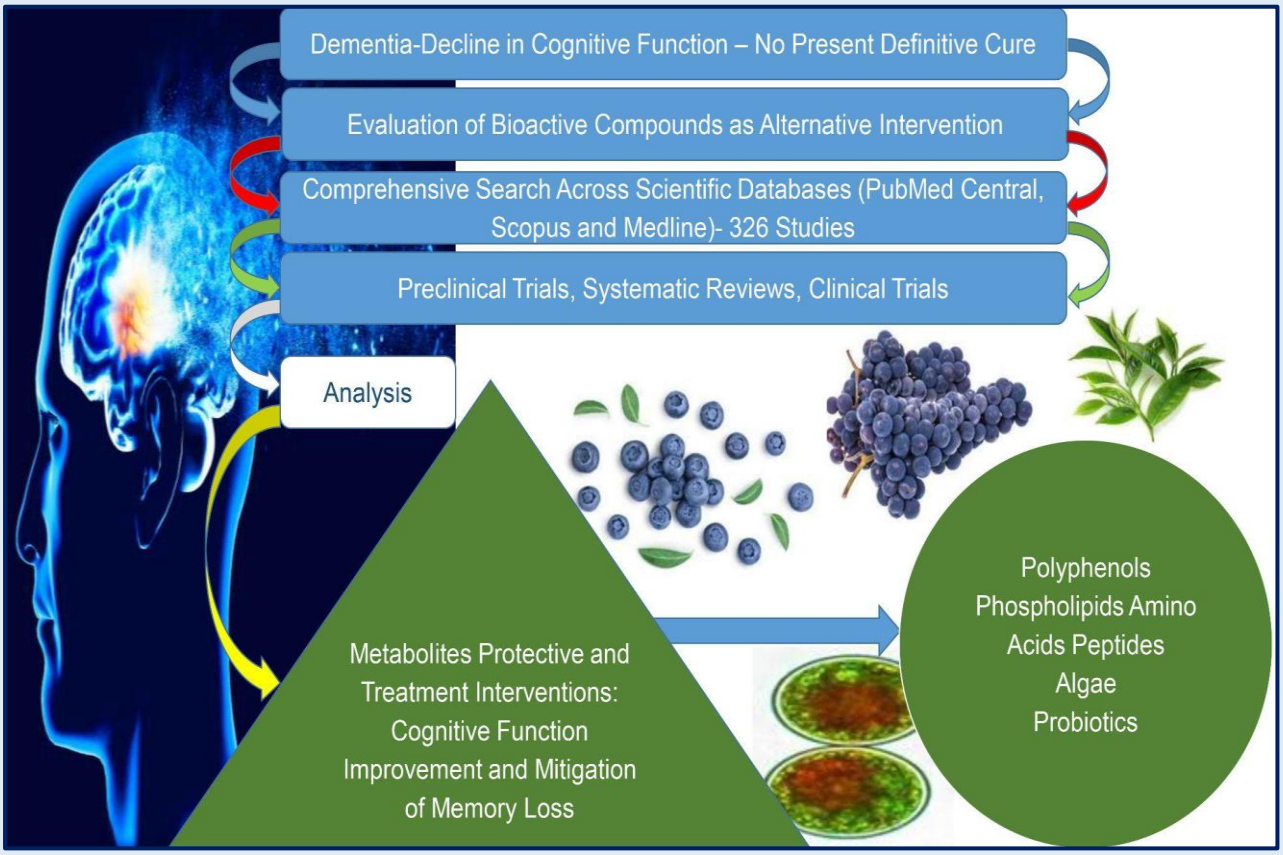
METHODS: A comprehensive search was conducted across scientific databases, including PubMed Central, Scopus, and Medline, resulting in the identification of 326 studies. The search strategy employed a combination of keywords such as

"food", "nutraceuticals", "extracts", "bioactive compounds", "dementia", "cognitive loss", "Alzheimer's", "geriatric", "elderly", and "seniors." To ensure the relevance of the selected studies, preclinical trials, systematic reviews, and clinical trials involving subjects without dementia were excluded. In this analysis, only 16 eligible studies were selected and reviewed, focusing on various categories of bioactive compounds, including polyphenols, phospholipids, amino acids and peptides, algae, and probiotics.

RESULTS: These studies highlighted these bioactive compounds as protective or treatment/management interventions that promise to improve cognitive function and mitigate memory loss in older adults. However, we identified some limitations that should be considered for future investigation.

CONCLUSION: Dementia is a complicated and unique disease that usually exists with comorbidities. Due to this, investigating the efficacy of alternative interventions may be challenging. While the number of studies evaluating several bioactive compounds for dementia continues to increase, there is still a dearth of information on their effect on people living with dementia. The mechanisms of action in most of the studies were speculated, and very few considered possible comorbidities common in people with dementia. We recommend that future investigations evaluate the efficacy of these interventions in more extended studies involving larger populations and diverse demographics and comorbidities.

Keywords: *Cognitive loss, dementia, elderly, geriatric, bioactive compounds, alternative medicine*



INTRODUCTION

Dementia is a widespread geriatric condition that impacts millions of individuals worldwide. According to the World Health Organization (WHO), over 55 million people globally are living with dementia as of 2022 (1). It is characterized by a progressive decline in cognitive abilities such as memory, thinking, judgment, and the ability to carry out daily activities. The most common cause of dementia is Alzheimer's disease, which constitutes approximately 70% of all cases (2).

While the specific causes of dementia are not fully understood, aging is the most significant known risk factor. Genetic factors and underlying health conditions such as diabetes, hypertension, and anxiety disorders are also believed to play a role (3). The pathological features of dementia include extracellular amyloid-β plaques and intracellular neurofibrillary tangles composed of tau protein in the brain (4). This neuronal damage and loss are thought to underlie the clinical symptoms.

Currently, there is no cure for dementia. Existing pharmacological treatments aim to manage symptoms and may provide temporary cognitive benefits but do little to slow disease progression (5). Commonly prescribed medications include cholinesterase inhibitors, NMDA receptor antagonists, and antidepressants. However, these drugs often cause adverse effects and do not stop dementia from worsening over time.

Due to the limitations of current therapies, there is an urgent need to develop effective and safer treatment strategies for dementia. Recently, bioactive compounds from natural sources termed “Functional Foods” have attracted interest as potential alternative or adjunct interventions. According to Martirosyan *et al.* (6), Functional food is defined as “Natural or processed foods that contain biologically active compounds, which, in defined, effective, non-toxic amounts, provide a clinically proven and documented health benefit utilizing specific biomarkers, to promote optimal health and reduce the risk of chronic/viral diseases and manage their symptoms.” A growing body of evidence suggests that certain phytochemicals may help protect against dementia by reducing neuroinflammation, improving neuronal signaling, and mitigating oxidative stress (7,8). However, limited clinical research has specifically examined their efficacy in individuals already diagnosed with dementia.

This systematic review aims to evaluate current evidence on established bioactive compounds that have demonstrated therapeutic effects for treating or managing mild cognitive impairment (MCI) and established dementia based on clinical studies involving human participants with these conditions. Focusing on individuals with cognitive decline, this analysis seeks to provide more applicable insights into using phytochemicals to manage dementia.

METHODOLOGY

Our search for studies began on the 2nd of June and ended on the 14th of July, 2023. Five independent researchers were involved in the search to avoid biases. We searched scientific and medical databases, including PubMed, Cochrane Library, and Medline, using several combinations of these keywords with advanced search: "food" OR "food" OR “extract” OR “natural” OR “compound” AND "memories" OR "memory" OR "cognitive" OR “cognition" AND "aged" OR "senior" OR "elderly" OR "older adult". Three hundred and twenty-six research results were first identified and were further filtered to include only randomized controlled trials, clinical trials, and studies including participants aged 65 years and above. Furthermore, all studies with participants without dementia, preclinical trials, and systematic reviews were excluded. The quality of the review was assessed using the AMSTAR 2 quality appraisal tool for

systematic reviews [9]. At the end of our search, only 17 eligible studies were selected for our review [10, 11, 12 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 24, 25]. These studies were divided into five subgroups based on classifications of bioactive compounds: phenols and polyphenols, phospholipids, amino acids and peptides, algae, and probiotics.

Table 1: Sources of bioactive compounds and their mechanisms of action against dementia

Bioactive Compound	Source	Mechanism of Action against Dementia	References
Flavonoids	Fenugreek seeds extract supplement	Neuroprotection, synaptic preservation, anti-inflammatory, inhibition of cognitive decline	[10], [29]
	Coffee and coffee cherry	Increases BDNF, antioxidative properties, reduce beta-amyloid plaques	[11], [30], [31], [32]
	Persicaria minora	Increases BDNF, improves neural function and mood	[12]
Anthocyanins	Grapes, berries	Modulates neuronal functions, improves cognitive functions, synaptic plasticity	[34]
	Concord grape juice	Improves working memory, increases cerebral blood flow	[13]
	Cherry juice	Improves memory, contains melatonin to promote antioxidant effects	[14], [15]
Resveratrol	Grapes, apples, plums, blueberries	Activates sirtuins, simulates caloric restriction, improves energy metabolism, prevents memory decline	[16], [17]
Lignans	Sesame oil cake extract	Prevents progression from MCI to dementia, improves verbal learning, decreases amyloid-β levels	[18]
Carotenoids	*Spirulina maxima*	Improves cognitive function, mitigates acetylcholinesterase activity, increases BDNF, ERK, CREB expression	[23]
Ganglioside	Deer antlers	Improves working memory, default mode network, protects against oxidative stress and neuronal damage	[19],[48], [49]
Phosphatidic acid and phosphatidylserine	Soy	Increases working memory score, slows progression of dementia	[20], [50]
L-theanine	Green tea, Black tea	Enhances brain alertness	[21]
Carnosine	Meat/muscle	Improves verbal episodic memory, suppresses expression of neurodegenerative factors	[22], [51]
Astaxanthin	Algae(*Haematococcus pluvalis*)	Improves psychomotor speed, processing speed, comprehension, decreases oxidative stress, elevates BDNF	[24]
Probiotics	*Lactobacillus plantarum*	Improves visual memory, induces anti-neuroinflammatory cytokines, inhibits the production of inflammatory cytokines	[25]

Phenols and Polyphenols: Phenols are found in most plants and are responsible for the taste (bitterness, astringency) and pigmentation of plant parts. Usually, they are biological agents that protect the plant against the environment, predators, and parasites [26]. Many studies have established that phenols are potent antioxidants and anti-aging agents that are beneficial to the prevention and treatment of several human conditions, including cardiovascular diseases, cancer, arthritis, ulcerative colitis, depression, and eye diseases [26-27]. Dietary phenols are proposed to be highly useful in preventing several neurodegenerative disorders through their antioxidant activities in preventing neuroinflammation and their effect on gut microbiota, intestinal catabolite synthesis, and brain homeostasis through the brain-gut axis [26-27].

Flavonoids: Fenugreek seeds are a rich source of flavonoids, with over 100mg/g [28]. Fenugreek seeds, which seem to exhibit strong pro-cholinergic activities [29], may prevent neuroinflammation and help preserve synapses and cholinergic neurons, thus improving memory and attention. A 4-month supplementation of fenugreek seed extract showed a reduction in blood pressure and malondialdehyde, a biomarker for oxidative stress, increased memory function, and improved mood in a cohort of seniors with Alzheimer's disease [9]. In a preclinical study, aluminum chloride-induced experimental Alzheimer's rats administered with fenugreek seed extract were found to be protected against aluminum overload, inhibiting the development of cognitive loss, anticholinesterase hyperactivity, beta-amyloid burden, and neuron death through the activation of the Akt/GSK3β pathway, which inhibits the expression of proinflammatory macrophages IL-12 and TNF-α [29].

Coffee cherry extract, a rich source of caffeine and other secondary metabolites, has been reported to be a potent antioxidant that increases brain-derived neurotrophic factor (BDNF), a crucial protein for neurogenesis, in 71 seniors with mild cognitive impairment (MCI) [11]. Numerous studies have suggested that coffee cherries possess neuroprotective activities. A preclinical study by Sallaberry *et al.* [30] previously confirmed that coffee cherry increased the hippocampal brain-derived neurotrophic factor (BDNF) levels by increasing proBDNF and cyclic adenosine 3',5'-monophosphate response element-binding (CREB) protein levels and reduced tropomyosin receptor kinase B (TrkB) levels in experimental rats. However, whether caffeine works synergistically with the other phytochemicals in coffee cherries is unclear. This is because Nrf2 regulates the transcription of BDNF. For context, an earlier study by *Higgins et al.* [31] mentioned that coffee cherry diterpenes cafestol and kahweol activated Nrf2-dependent proteasomal activities associated with protecting against beta-amyloid neurotoxicity in both glial and nerve cells. Additionally, Gardener *et al.* [32] explained that crude caffeine consumption reduced beta-amyloid plaques of type 41 and 42 in the hippocampus of Alzheimer's disease rats. In another rodent model study, Zhang *et al.* [33] demonstrated that chlorogenic acid (CGA), another phytochemical found in coffee cherry, increased neurotransmission by activating synaptic transmission genes and upregulating neuroactive ligand-receptor interaction and cholinergic signaling pathways. This may indicate that there is a synergistic effect of many phytochemicals, as caffeine may contribute partially to cognitive improvement.

Another polyphenol-rich extract, Persicaria minor [12], increased BDNF in seniors struggling with MCI for 6 months. Lau *et al.* [12] explained that this increase resulted from the activation of BDNF-TrKB and similar pathways. Additionally, the study reported the activation of the dorsolateral prefrontal cortex with an improvement in the participants' visual brain task and mood.

Anthocyanins: Grapes and berries, sources rich in anthocyanins, have gained significant attention in dietary therapies for dementia research. Anthocyanin-rich foods play a role in modulating neuronal functions and improving working memory, learning, and cognitive motor function by inhibiting IL-1β and TNF-kappa B [34]. These bioactive compounds also exhibit modulatory effects by improving structural and synaptic plasticity markers [34].

Concord grape juice, a potent source of anthocyanins and flavonols, was studied for its neurocognitive-promoting activities in older adults with mild cognitive impairment for 16 weeks [13]. The study observed activation in the right middle prefrontal and superior middle parietal lobes, resulting in a noticeable improvement in working memory. Furthermore, the flavonol content of Concord grape juice was suggested to have improved the observed cerebral blood flow, which was reflected in the increase in neural recruitment.

In addition to grapes and berries, Kent *et al.* [14] assessed participants older than 70 who had mild cognitive impairment after consuming cherry juice. After the 6th and 12th weeks of daily consumption, verbal fluency, short-term memory, and long-term memory improved. Additionally, cherries contain melatonin, which is reported to mitigate nitric oxide synthase and promote the production of antioxidant enzymes [14].

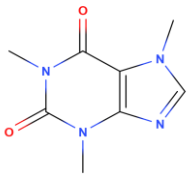
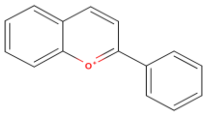
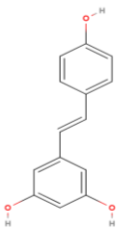
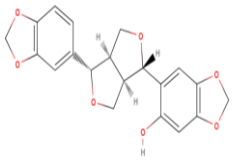
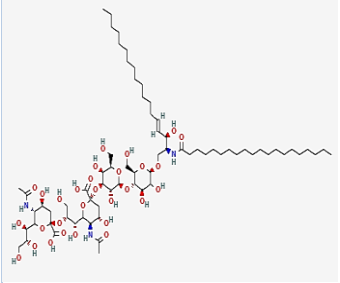
Resveratrol: Resveratrol (3, 5, 4'-trihydroxystilbene) is a non-flavonoid polyphenol that naturally occurs in grapes, apples, plums, blueberries, and peanuts. Sawda *et al.* [16] demonstrated that resveratrol activates sirtuins, which are NAD+-dependent deacetylases responsible for energy metabolism, genome stability, and repair. This activation simulates caloric restriction to prevent aging and loss of memory function in seniors with mild to moderate Alzheimer's disease.

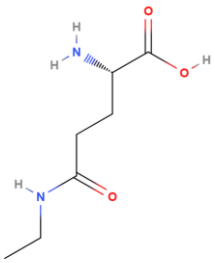
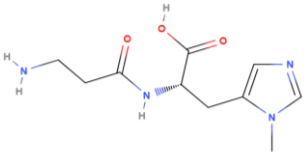
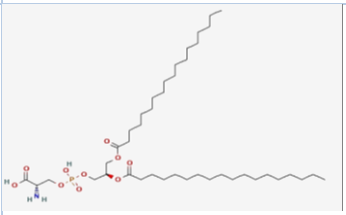
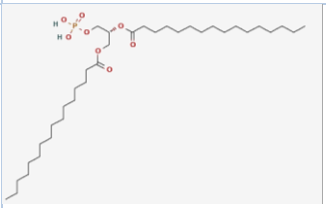
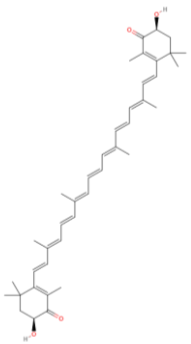
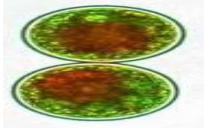
Lee *et al.* [17] supplemented ten subjects with mild cognitive impairment, with an average age of 72 years, with resveratrol for six months. The study showed an improvement in energy metabolism in the right superior temporal cortex compared to the placebo group, which experienced a decrease in the left prefrontal, cingulate, and left superior posterolateral temporal cortex.

Lignans: Lignans play versatile roles in combating dementia. Numerous studies have proven their antimicrobial, anti-inflammatory, and antioxidative properties and their ability to attenuate cell death, antagonize NMDA receptors, mitigate anticholinesterase activity, and strengthen nerve protection [35].

In a study by Jung *et al.* [18] involving sesame oil cake extract, a lignan known as sesaminol was found to hinder the progression from mild cognitive impairment to dementia. The study documented significant improvements in verbal learning and a notable decrease in amyloid-β and plasma amyloid-β (1–42) levels in the treatment group compared to the placebo group, further highlighting the significant role of lignans in dementia prevention

Table 2: Neuroprotective Bioactive Compounds

Bioactive Compound	Structure	Molecular Formula	Biological Source
Caffeine	 [36]	$C_8H_{10}N_4O_2$	 Coffee Cherry[1]
Anthocyanin	 [37]	$C_{15}H_{11}O^+$	 Blueberries[1]
Resveratrol	 [38]	$C_{14}H_{12}O_3$	 Concord grape[1]
Sesaminol	 [39]	$C_{20}H_{18}O_7$	 Sesame seeds[1]
Ganglioside	 [40]	$C_{72}H_{129}N_3O_{29}$	 Deer Antlers [1]

L-theanine	 [41]	$C_7H_{14}N_2O_3$	 Tea leaves [1]
Carnosine	 [42]	$C_9H_{14}N_4O_3$	 Beef Muscle[1]
Anserine	 [43]	$C_{10}H_{16}N_4O_3$	 Tuna[1]
Phosphatidylserine	 [44]	$C_{42}H_{82}NO_{10}P$	 Soy lecithin[1]
Phosphatidic acid	 [45]	$C_{35}H_{69}O_8P$	 Soy lecithin[1]
Astaxanthin	 [46]	$C_{40}H_{52}O_4$	 Microscopic view of *Haematococcus pluvalis*[1]

Source[1]: Unsplash [47]

Lipid and Phospholipids: Some bioactive compounds from lipid and phospholipid sources have been found to have neuroprotective activities. We reviewed a randomized clinical controlled trial by Jeon *et al.* [19] that meticulously examined the neuroprotective and memory-enhancing properties of ganglioside, a glycosphingolipid containing sialic acid, in study subjects with subjective cognitive impairment. Ganglioside, also known as deer antler extract, has historically been used as an anti-aging ingredient in traditional Korean medicine [48]. In a study by Jeon *et al.* [19], high and low dosages of ganglioside oral supplements resulted in improved working memory performance and the default mode network of its study subjects. Although the action mechanism of ganglioside was not documented in the study, the bioactive compound may have potent restorative and therapeutic properties for treating dementia and related cognitive conditions, as demonstrated in previous preclinical studies. Kim *et al.* [48] pretreated mouse hippocampal cells (HT-22 cells) with ganglioside before stimulating them with glutamate to induce cell death. Ganglioside inhibited cell death by preventing lactate dehydrogenase leakage, oxidative stress through reactive oxygen species and lipid peroxidation, and decreased glutathione levels and glutathione peroxidase activity. In another study by Du *et al.* [49], mice orally administered ganglioside for 14 days and scopolamine showed inhibited acetylcholinesterase activities, decreased GSH levels, and prevented oxidative damage to neurons in hippocampal CA1 and CA3 regions.

Fifty-six patients diagnosed with mild memory impairment and definite Alzheimer's disease were supplemented with soy lecithin (300mg of phosphatidylserine and 270mg of phosphatidic acid) for six months [20]. The study revealed a slightly significant increase in working memory scores, particularly in information processing, visual memory, and memorizing numbers in the treatment group compared to the placebo group. Li *et al.* [50] demonstrated in an animal model experiment that soy lecithin, when administered with soy isoflavone, protected the cerebrovascular endothelial cells through improved cerebral blood flow. While the efficacy of soy lecithin for dementia is yet to be confirmed, it is worth noting that lecithin is a rich source of choline, which may slow the progression of dementia.

Amino Acids and Peptides: L-theanine, a protein commonly found in green tea and black tea, is suggested to possess neurocognitive enhancement properties. Park *et al.* [22] reported that a single dose of L-theanine, in combination with catechin from green tea extract, enhanced brain alertness due to increased activity in the temporal, frontal, parietal, and occipital lobes just three hours after administration.

Carnosine and its methylated form, anserine, are dipeptides abundantly found in the skeletal muscle of chicken, salmon, rabbit, beef, and turkey. They have been reported to play an essential role in preventing several diseases, including neurological disorders and age-related diseases, by improving the activation of monocytes, macrophages, and other immunoprotective cells [51]. Katakura *et al.* [22] reported an improvement in verbal episodic memory in 60 subjects between the ages of 60 and 70 after 3 months of supplementation with 1g of anserine and carnosine (3:1). The study explained that anserine-carnosine supplementation suppressed the expression of the C-C Motif Chemokine Ligand 24 (CCL24), an eotaxin associated with neurodegeneration through an unknown pathway.

Algae: Choi *et al.* [23] evaluated the effect of *Spirulina maxima* extract (SM70EE) on cognitive improvement in older adults with MCI for 12 weeks. Spirulina maxima is an abundant microscopic cyanobacterium that has been used as food among pre-Columbian

Mesoamerican communities [532 It is low in toxins and has been identified for its immunoprotective functions against several diseases. Microalgae were reported to reduce the progression of Alzheimer's disease through the improvement in visual learning and visual working memory tests [23]. A proposed action mechanism of spirulina is the mitigation of acetylcholinesterase activity and the improved expression of BDNF, extracellular signal-regulated kinases (ERK), and cyclic adenosine 3',5'-monophosphate response element-binding protein (CREB) [23].

Astaxanthin, a carotenoid extracted from the microalgae *Haematococcus pluvialis*, is found to possess strong antioxidant and immunomodulatory properties. Ito *et al.* [24] supplemented healthy adults with mild cognitive impairment with 8 mg of astaxanthin-sesamin. The study reported improvements in psychomotor speed, processing speed, and comprehension. It further explained that there was a decrease in oxidative stress and elevated levels of BDNF. However, it remains unclear whether this effect is solely due to astaxanthin, sesamin, or the synergistic effect of both.

Probiotics: Probiotics are speculated to be a potent dietary intervention for dementia due to their activities in the gut-brain axis. The proposed mechanism of action of probiotics against dementia is through immune modulation, activation of endocrine pathways, and neuronal regulation [6]. Sakurai *et al.,* [25] studied *Lactobacillus plantarum* (OLL2712), a lactic acid bacterium readily available in various fermented foods, for its effect on memory functions in 78 individuals with MCI. The study recorded a significant improvement in visual memory among study participants compared to the placebo group. It has been confirmed that OLL2712 has the highest inducibility of IL-10, a potent anti-neuroinflammatory cytokine. IL-10 inhibits the production of TNF-α, IL-1β, IL-6, and interferon-γ inflammatory cytokines in the brain's oligodendrocytes, astrocytes, and microglia [25].

Limitations of Study and Future Directions: Despite the promising efficacy of these bioactive compounds, we identified limitations in the reviewed works that should be subject to further investigation. All studies reported the effects of their interventions on study subjects struggling with different stages of memory decline. However, most of them focused on suppressing symptoms and did not demonstrate the mechanisms of action of the bioactive compounds. This may be due to the multiple speculations about the pathogenesis of dementia, which are still largely under study. Interventions like these should be studied for prolonged periods to deduce their efficacy in the short and long-term periods of use. The longest duration among all the reviewed studies is 52 weeks, with 80% concluding within 2-4 months and the shortest being 28 days. It is common for individuals living with dementia to have underlying conditions that may vary between populations. These conditions are not mentioned or considered in all the studies. This could be due to the challenges associated with organizing studies involving study subjects with health conditions, as altered outcomes could be a concern. Therefore, we recommend studies with larger study populations to understand the effects of these interventions, considering factors such as sex, age range, ethnicity, and existing comorbidities. Additionally, it remains imperative that the signaling pathways and receptor targets involved in the development of dementia are well understood to elucidate the interactions and effects of the proposed interventions.

Functional foods-based intervention is currently a developing body of science with soaring popularity among consumers. It is now a known fact that functional foods can indeed offer substantial remedial and therapeutic benefits to several diseases. Unfortunately, it has not been duly recognized as a

viable option by most health and drug regulatory bodies [6, 53]. The unregulated use of functional foods for self-medication is becoming popular among consumers who seek health information from unconventional sources such as the Internet. Regulatory bodies must acknowledge functional food-based interventions for disease management and cure through the standardization and establishment of safe limits to ensure the correct and risk-free use among consumers.

Conclusion and Recommendation: With over 55 million individuals living with dementia, this debilitating condition is still critically understudied. Dementia is a complex and unique condition with no existing cure. Our study highlights bioactive compounds that may be useful and cost-effective for dementia treatment and management. The novelty of this study is our focus on current limitations hindering natural product research for dementia care. With a careful selection of high-quality scientific research, our study gives a condensed view of current interventions and a guide to future leads in alternative dementia care with natural products.

List of Abbreviations: WHO: World Health Organization, NMDA: N-Methyl-D-Aspartate, MCI: Mild Cognitive Impairment, AMSTAR 2: A Measurement Tool to Assess Systematic Reviews 2, BDNF: Brain-Derived Neurotrophic Factor, ERK: Extracellular Signal-Regulated Kinase, CREB expression: cAMP Response Element-Binding Protein expression, Akt/GSK3ß: Protein Kinase B/Glycogen Synthase Kinase 3 beta, IL-2: Interleukin-2, TNF-alpha: Tumor Necrosis Factor-alpha, TrkB: Tropomyosin Receptor Kinase B, Nrf2-dependent: Nuclear factor erythroid 2-related factor 2-dependent, IL-1ß: Interleukin-1 beta, TNF-Kappaß: Tumor, Necrosis Factor-Kappa B, NAD+: Nicotinamide Adenine Dinucleotide, HT-22 cells: A cell line derived from mouse hippocampal neurons, GSH: Glutathione, CA1: Cornu Ammonis 1 (region of the hippocampus), CA3: Cornu Ammonis 3 (region of the hippocampus), CCL24: Chemokine (C-C motif) ligand 24, SM70EE: *Spirulina maxima*, 1L-6: Interleukin-6, IL-10: Interleukin-10, TBARS: Thiobarbituric Acid Reactive Substances, AOPP: Advanced Oxidation Protein Products

Competing Interests: The authors have no financial interests or other conflicts of interest to disclose.

Authors' Contributions: Authors' contributions: Nicholas-Okpara, V.A.N. designed the review, supervised and prepared the manuscript; Adegboyega, M. O. prepared and revised the manuscript; Oben, J.E. revised the manuscript; Williams, L.L. revised the manuscript, Utazi, I. A., Rhema, J., Akanno, C. and Ubaka A.J. assisted in scholarly journals search. All authors read and approved the final version before its submission.

REFERENCES

1. World Health Organization. Dementia. [Online] Available: https://www.who.int/news-room/fact-sheets/detail/dementia [Accessed 16th August 2023].
2. Błaszczyk JW: Pathogenesis of Dementia. International Journal Molecular Sciences. 2022 Dec 29; 24(1): 543. DOI: https://doi.org/10.3390/ijms24010543
3. Cao Q, Tan CC, Xu W, Hu H, Cao XP, Dong Q, Tan L, Yu JT: The Prevalence of Dementia: A Systematic Review and Meta-Analysis. Journal of Alzheimer's Disease. 2020; 73(3): 1157-1166. DOI: https://doi.org/10.3233/JAD-191092
4. Emmady PD, Schoo C, Tadi P: Major Neurocognitive Disorder (Dementia) [Updated 2022 Nov 19]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 January.
5. Dave BP, Shah YB, Maheshwari KG, Mansuri KA, Prajapati BS, Postwala HI, Chorawala MR. Pathophysiological Aspects and Therapeutic Armamentarium of Alzheimer's Disease: Recent Trends and Future Development. Cellular and Molecular Neurobiology, 2023; 43(8): 3847-3884. https://www.doi.org/10.1007/s10571-023-01408-7

6. Martirosyan D., Kanya H., Nadalet C. Can functional foods reduce the risk of disease? Advancement of functional food definition and steps to create functional food products. Functional Foods in Health and Disease 2021; 11(5): 213-221. DOI: https://www.doi.org/10.31989/ffhd.v11i5.788
7. Abubakar MB, Sanusi KO, Ugusman A, Mohamed W, Kamal H, Ibrahim NH, Khoo CS, Kumar J. Alzheimer's Disease: An Update and Insights Into Pathophysiology. Frontiers in Aging Neuroscience. 2022 Mar 30; 14: 742408. DOI: https://doi.org/10.3389/fnagi.2022.742408
8. Padda, IS, Parmar, M. Aducanumab. In StatPearls. StatPearls Publishing. 2023 Jun 3.
9. Shea, B. J., Reeves, B. C., Wells, G., Thuku, M., Hamel, C., Moran, J., Moher, D., Tugwell, P., Welch, V., Kristjansson, E., & Henry, D. A. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017 Sep 21; 358: j4008 DOI: https://doi.org/10.1136/bmj.j4008
10. Foroumandi E, Javan R, Moayed L, Fahimi H, Kheirabadi F, Neamatshahi M, et al: The effects of fenugreek seed extract supplementation in patients with Alzheimer's disease: A randomized, double-blind, placebo-controlled trial. Phytotherapy Research. 2023 Jan; 37(1): 285-294. DOI: https://doi.org/10.3389/fnagi.2022.742408
11. Robinson JL, Hunter JM, Reyes-Izquierdo T, Argumedo R, Brizuela-Bastien J, Keller R, et al: Cognitive short- and long-term effects of coffee cherry extract in older adults with mild cognitive decline. Neuropsychology Development and Cognition. Section B, Aging, Neuropsychology and Cognition. 2020 Nov; 27(6): 918-934. DOI: https://doi.org/10.1080/13825585.2019.1702622
12. Lau H, Shahar S, Mohamad M, Rajab NF, Yahya HM, Din NC, et al: The effects of six months Persicaria minor extract supplement among older adults with mild cognitive impairment: a double-blinded, randomized, and placebo-controlled trial. BMC Complementary Medicine and Therapies. 2020 Oct 19; 20(1): 315. DOI: https://doi.org/10.1186/s12906-020-03092-2
13. Krikorian R, Boespflug EL, Fleck DE, Stein AL, Wightman JD, Shidler MD, et al: Concord grape juice supplementation and neurocognitive function in human aging. Journal of Agriculture and FKent K, Charlton KE, Netzel M, Fanning K: Food-based anthocyanin intake and cognitive outcomes in human intervention trials: a systematic review. Journal of Human Nutrition and Dietetics. 2017 Jun;30(3):260-274. Chemistry. 2012 Jun 13; 60(23): 5736-42. DOI: https://doi.org/10.1021/jf300277g
14. Kent K, Charlton K, Roodenrys S, Batterham M, Potter J, Traynor V, et al: Consumption of anthocyanin-rich cherry juice for 12 weeks improves memory and cognition in older adults with mild-to-moderate dementia. European Journal of Nutrition. 2017 Feb; 56(1): 333-341. DOI: https://doi.org/10.1007/s00394-015-1083-y
15. Chai SC, Jerusik J, Davis K, Wright RS, Zhang Z: Effect of Montmorency tart cherry juice on cognitive performance in older adults: a randomized controlled trial. Food & Function. 2019 Jul 17; 10(7): 4423-4431. DOI: https://doi.org/10.1039/c9fo00913b
16. Sawda C, Moussa C, Turner RS: Resveratrol for Alzheimer's disease. Annals of New York Academy of Sciences. 2017 Sep; 1403(1): 142-149. DOI: https://doi.org/10.1111/nyas.13431
17. Lee J, Torosyan N, Silverman DH: Examining the impact of grape consumption on brain metabolism and cognitive function in patients with mild decline in cognition: A double-blinded placebo controlled pilot study. Experimental Gerontology. 2017 Jan; 87(Pt A): 121-128. DOI: https://doi.org/10.1016/j.exger.2016.10.004
18. Jung SJ, Jung ES, Ha KC, Baek HI, Park YK, Han SK, et al: Efficacy and safety of sesame oil cake extract on memory function improvement: A 12-Week, randomized, double-blind, placebo-controlled pilot study. Nutrients. 2021 Jul 28; 13(8): 2606. DOI: https://doi.org/10.3390/nu13082606
19. Jeon, Y., Kim, B., Kim, J. E., Kim, B. R., Ban, S., Jeong, J. H., et al:. Effects of Ganglioside on Working Memory and the Default Mode Network in Individuals with Subjective Cognitive Impairment: A Randomized Controlled Trial. The American journal of Chinese medicine. 2016 April 25; 44(3): 489–514. DOI: https://doi.org/10.1142/S0192415X16500270
20. Moré MI, Freitas U, Rutenberg D: Positive effects of soy lecithin-derived phosphatidylserine plus phosphatidic acid on memory, cognition, daily functioning, and mood in elderly patients with Alzheimer's disease and dementia. Advances in Therapy. 2014 Dec; 31(12): 1247-62. DOI: https://doi.org/10.1007/s12325-014-0165-1
21. Park SK, Jung IC, Lee WK, Lee YS, Park HK, Go HJ, et al: A combination of green tea extract and l-theanine improves memory and attention in subjects with mild cognitive impairment: a double-blind placebo-controlled study. Journal of Medicinal Food. 2011 Apr; 14(4): 334-43. DOI: https://doi.org/10.1089/jmf.2009.1374
22. Katakura Y, Totsuka M, Imabayashi E, Matsuda H, Hisatsune T: Anserine/Carnosine supplementation suppresses the expression of the inflammatory chemokine CCL24 in peripheral blood mononuclear cells from elderly people. Nutrients. 2017 Oct 31; 9(11): 1199.

DOI: https://doi.org/10.3390/nu9111199

23. Choi WY, Lee WK, Kim TH, Ryu YK, Park A, Lee YJ, et al: The effects of spirulina maxima extract on memory improvement in those with mild cognitive impairment: A randomized, double-Blind, placebo-controlled clinical trial. Nutrients. 2022 Sep 9; 14(18): 3714. DOI: https://doi.org/10.3390/nu14183714
24. Ito N, Saito H, Seki S, Ueda F, Asada T: Effects of composite supplement containing astaxanthin and sesamin on cognitive functions in people with mild cognitive impairment: A randomized, double-blind, placebo-controlled trial. Journal of Alzheimer's Disease. 2018; 62(4): 1767-1775. DOI: https://doi.org/10.3233/JAD-170969
25. Sakurai K, Toshimitsu T, Okada E, Anzai S, Shiraishi I, Inamura N, et al: Effects of Lactiplantibacillus plantarum OLL2712 on memory function in older adults with declining memory: A randomized placebo-controlled trial. Nutrients. 2022 Oct 14; 14(20): 4300. DOI: https://doi.org/10.3390/nu14204300
26. Matsumura Y, Kitabatake M, Kayano SI, Ito T. Dietary phenolic compounds: their health benefits and association with the gut microbiota. Antioxidants (Basel). 2023 April 4; 12(4): 880. DOI: https://doi.org/10.3390/antiox12040880
27. Li Y, Peng Y, Shen Y, Zhang Y, Liu L, Yang X. Dietary polyphenols: Regulate the advanced glycation end products-RAGE axis and the microbiota-gut-brain axis to prevent neurodegenerative diseases. Critical Reviews in Food Science and Nutrition. 2023; 63(29): 9816-9842. DOI: https://doi.org/10.1080/10408398.2022.2076064
28. Srivastava A, Singh Z, Verma V, Choedon T. Potential health benefits of fenugreek with multiple pharmacological properties. In Research Anthology on Recent Advancements in Ethnopharmacology and Nutraceuticals. 2022; 672-687. IGI Global.
29. Norouzkhani N, Karimi AG, Badami N, Jalalifar E, Mahmoudvand B, Ansari, A, Sariyarighan NP, Alijanzadeh D, Aghakhani S, Shayestehmehr R, Arzaghi M, Sheikh Z, Salami Y, Marabi MH, Abdi A, Deravi N. From kitchen to clinic: Pharmacotherapeutic potential of common spices in Indian cooking in age-related neurological disorders. Frontiers in pharmacology, 2022; 13: 960037. DOI: https://doi.org/10.3389/fphar.2022.960037
30. Sallaberry C, Nunes F, Costa MS, Fioreze GT, Ardais AP, Botton PH, et al: Chronic caffeine prevents changes in inhibitory avoidance memory and hippocampal BDNF immunocontent in middle-aged rats. Neuropharmacology. 2013 Jan; 64: 153-9. DOI: https://doi.org/10.1016/j.neuropharm.2012.07.010
31. Higgins LG, Cavin C, Itoh K, Yamamoto M, Hayes JD: Induction of cancer chemopreventive enzymes by coffee is mediated by transcription factor Nrf2. Evidence that the coffee-specific diterpenes cafestol and kahweol confer protection against acrolein. Toxicology and Applied Pharmacology. 2008 Feb 1; 226(3): 328-37. DOI: https://doi.org/10.1016/j.taap.2007.09.018
32. Gardener SL, Rainey-Smith SR, Villemagne VL, Fripp J, Doré V, Bourgeat P, et al; AIBL Investigators: Higher coffee consumption is associated with slower cognitive decline and less cerebral Aβ-Amyloid accumulation over 126 months: data from the Australian imaging, biomarkers, and lifestyle study. Frontiers in Aging Neuroscience. 2021 Nov 19; 13: 744872. DOI: https://doi.org/10.3389/fnagi.2021.744872
33. Zhang SQ, Tian D, Hu CY, Meng YH. Chlorogenic Acid Ameliorates High-Fat and High-Fructose Diet-Induced Cognitive Impairment via Mediating the Microbiota–Gut–Brain Axis. Journal of Agricultural and Food Chemistry, 2022; 70(8): 2600-2615. https://doi.org/10.1021/acs.jafc.1c07479
34. Kent K, Charlton KE, Netzel M, Fanning K: Food-based anthocyanin intake and cognitive outcomes in human intervention trials: a systematic review. Journal of Human Nutrition and Dietetics. 2017 Jun; 30(3): 260-274. DOI: https://doi.org/10.1111/jhn.12431
35. Han N, Wen Y, Liu Z, Zhai J, Li S, Yin J: Advances in the roles and mechanisms of lignans against Alzheimer's disease. Frontiers in Pharmacology. 2022 Oct 12; 13: 960112. DOI: https://doi.org/10.3389/fphar.2022.960112
36. National Center for Biotechnology Information. PubChem Compound Summary for CID 2519, Caffeine. [https://pubchem.ncbi.nlm.nih.gov/compound/Caffeine]. Retrieved August 22, 2023
37. National Center for Biotechnology Information. PubChem Compound Summary for CID 145858, Flavylium. [https://pubchem.ncbi.nlm.nih.gov/compound/Flavylium] Retrieved August 22, 2023
38. National Center for Biotechnology Information. PubChem Compound Summary for CID 94672, Sesaminol. [https://pubchem.ncbi.nlm.nih.gov/compound/Sesaminol] Retrieved August 22, 2023
39. National Center for Biotechnology Information. PubChem Compound Summary for CID 20057325, Ganglioside GD3 (d18:1/20:0). [https://pubchem.ncbi.nlm.nih.gov/compound/Ganglioside-GD3-_d18_1_20_0] Retrieved August 22, 2023
40. National Center for Biotechnology Information. PubChem Compound Summary for CID 439378, Theanine.[https://pubchem.ncbi.nlm.nih.gov/compound/Theanine] Retrieved August 22, 2023

41. National Center for Biotechnology Information. PubChem Compound Summary for CID 112072, Anserine. [https://pubchem.ncbi.nlm.nih.gov/compound/Anserine] Retrieved August 23, 2023
42. National Center for Biotechnology Information. PubChem Compound Summary for CID 439224, Carnosine. [https://pubchem.ncbi.nlm.nih.gov/compound/Carnosine] Retrieved August 22, 2023
43. National Center for Biotechnology Information. PubChem Compound Summary for CID 112072, Anserine. [https://pubchem.ncbi.nlm.nih.gov/compound/Anserine] Retrieved August 23, 2023
44. National Center for Biotechnology Information. PubChem Compound Summary for CID 446066, 2-(Hexadecanoyloxy)-1-[(phosphonooxy)methyl]ethyl hexadecanoate. [https://pubchem.ncbi.nlm.nih.gov/compound/1_2-Dipalmitoyl-sn-glycerol-3-phosphate] Retrieved August 23, 2023
45. National Center for Biotechnology Information. PubChem Compound Summary for CID 9547096, Phosphatidylserine. Retrieved August 23, 2023 from https://pubchem.ncbi.nlm.nih.gov/compound/Phosphatidylserine.
46. National Center for Biotechnology Information. PubChem Compound Summary for CID 5281224, Astaxanthin.[https://pubchem.ncbi.nlm.nih.gov/compound/Astaxanthin] Retrieved August 23, 2023
47. Unsplash. 2023. [https://unsplash.com/] Accessed 23 August 2023
48. Kim CR, Jeon HL, Shin SK, Kim HJ, Ahn CW, Jung SU et al: Neuroprotective action of deer bone extract against glutamate or $A\beta_{1-42}$-induced oxidative stress in mouse hippocampal cells. Journal of Medicinal Food. 2014 Feb; 17(2): 226-35. DOI: https://doi.org/10.1089/jmf.2013.2951
49. Du CN, Min AY, Kim HJ, Shin SK, Yu HN, Sohn EJ, et al: Deer bone extract prevents against scopolamine-induced memory impairment in mice. Journal of Medicinal Food. 2015 Feb; 18(2): 157-65. DOI: https://doi.org/10.1089/jmf.2014.3187
50. Li H, Wang X, Li X, Zhou X, Wang X, Li T, Xiao R, Xi Y. Role of soy lecithin combined with soy isoflavone on cerebral blood flow in rats of cognitive impairment and the primary screening of its optimum combination. Nutrition Research and Practice, 2023; 17(2): 371-385. DOI: https://doi.org/10.4162/nrp.2023.17.2.371
51. Wu G: Important roles of dietary taurine, creatine, carnosine, anserine and 4-hydroxyproline in human nutrition and health. Amino Acids. 2020 Mar; 52(3): 329-360. DOI: https://doi.org/10.1007/s00726-020-02823-6
52. Trotta T, Porro C, Cianciulli A, Panaro MA: Beneficial effects of spirulina consumption on brain health. Nutrients. 2022 Feb 5;14(3):676. DOI: https://doi.org/10.3390/nu14030676
53. Martirosyan, D. M., Stratton S. Advancing functional food regulation. Bioactive Compounds in Health and Disease 2023; 6(7): 166-171. DOI: https://www.doi.org/10.31989/bchd.v6i7.1178