# Role of Natural Products in Mitigating Oxidative Stress associated with Alzheimer's Disease

Rajdip Ghosh[1], Rochit Hatua[2], Biplab Das[3], Sk Sangram[4], Anamitra Bhattacharya[5], Sayani Paul[6]
[1,2] *Final year Bachelor in pharmacy student at Calcutta Institute of Pharmaceutical Technology and AHS.*
[3] *Assistant professor of Pharmacognosy Department at Calcutta Institute of Pharmaceutical Technology & AHS.*
[4] *Assistant professor of Pharmaceutical Chemistry Department at Calcutta Institute of Pharmaceutical Technology & AHS.*
[5] *Assistant Professor Department of Pharmacology at Jakir Hossain Institute of Pharmacy.*
[6] *Assistant professor Department of Pharmaceutical Chemistry at Bengal School of Technology.*

Graphical Abstract:

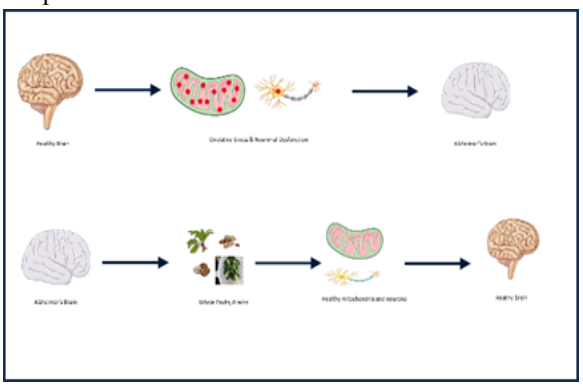


Figure 01: Graphical abstract shows how a healthy brain got effected as AD brain and AD brain got treated with natural products and shows anti AD activity

***Abstract*—The most prevalent type of dementia in the world, Alzheimer's disease, has a major impact on a patient's ability to do daily duties. It is well recognized that plant products offer a variety of distinct and innovative secondary metabolites. The published study articles about the anti-Alzheimer's effects of natural plant products, such as seeds, fruits, roots, etc., are the main topic of this review. Alkaloids, peptides, terpenoids, and steroids are among the naturally natural compounds that are examined according to their structure and classification. The specifics of these natural compounds' classification, occurrence, and bioactivities from a range of natural sources.**

***Index Terms*—Alzheimer's, natural products, secondary metabolites**

## I. INTRODUCTION

The most prevalent cause of dementia globally, Alzheimer's disease (AD), is a progressive neurological illness that impairs cognition, thinking, behaviour, even daily functioning. Alzheimer's disease is thought to be primarily caused by aberrant beta-amyloid and phosphorylated tau protein buildup, as well as nerve cell destruction. The most recent WHO data estimates that 35.6 million individuals worldwide suffered from dementia in 2010; by 2050, that number could have tripled. The largest risk factor for Alzheimer's dementia is age, which significantly raises the disease's incidence and death rate and places a significant burden on families and society as a whole. For those over 65, the frequency of dementia ranged from 5.0 to 13.1%; for persons aged over 85, this percentage climbed to 33.2%. And the mortality rate rose by 78% for those 80 years of age and above, and by 33–51% for those over 65. Memantine, donepezil, rivastigmine, tacrine, galantamine, and aducanumab are among the few treatment medicines that have been made clinically available for this illness. These medications can alleviate moderate cognitive impairment symptoms associated with AD, but they cannot stop the disease's progression to achieve the best possible treatment outcomes. In order to prevent and slow the disease's course, enhance cognitive function, and lessen behavioural issues in AD patients, it is imperative that novel treatments be developed.

From ancient times, various continents have used plant-based natural products as a treatment for Alzheimer's disease. Certain Plants produce novel bioactive substances with distinctive structures, including quinones, lactones, phenols, alkaloids, steroids, terpenoids, and other compounds. Among other things, these separated metabolites exhibit antibacterial, antioxidant, anti-inflammatory, antiviral, and anti-Alzheimer's characteristics.

This research conducts a thorough analysis of all major compounds with anti-Alzheimer ’s-related properties that were obtained from various plant sources. These substances, which are primarily alkaloids, peptides, polyketides, terpenoids, and steroids, are categorized according to their structural skeleton. These metabolites are particularly studied for their antioxidant properties, neuroprotective effects, suppression of butyrylcholinesterase (BChE) and acetylcholinesterase (AChE).

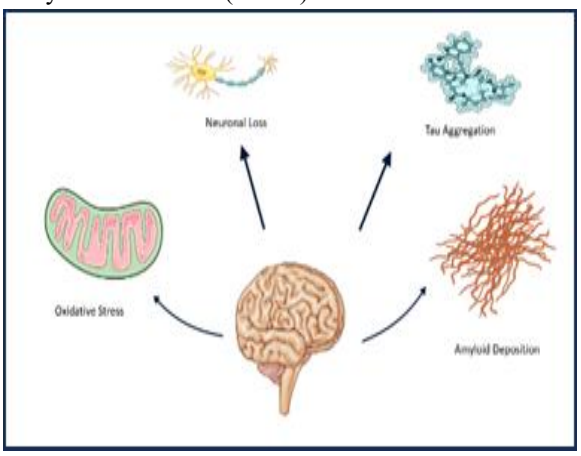



Figure 02 – General Causes of AD ( oxidative stress, neuronal loss, tau aggregation and Amyloid Deposition that are the main causes of AD)

1.1 Oxidative Stress supposition of Alzheimer’s Disease

Numerous researches were conducted to examine the pathophysiology of AD; nevertheless, the complexity of the disease and its physiological and psychological side effects have made it extremely difficult to clarify(Noori T et al, 2021). The precise pathophysiology of AD is currently unclear. Cholinergic, tau protein, β-Amyloid protein, oxidative stress, and other theories are the primary aetiology hypotheses for AD (Du X et al, 2018).

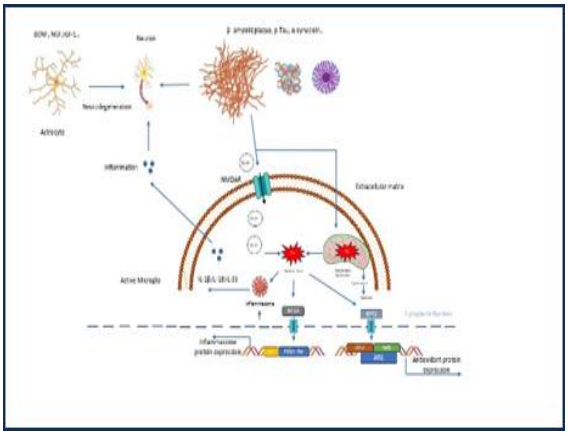


Figure 03: Common and major pathways in CNS diseases—biological processes, including oxidative stress, neuroinflammation, and mitochondrial dysfunction —have been implicated in the development and pathogenesis of CNS diseases. Li et al

The development of ROS and oxidative stress reactions serves as an empirical basis for the oxidative stress hypothesis(Patrico D et al, 2008). Numerous active metal ions, particularly Copper, Zinc, and Iron, are out of balance in AD pathogenic circumstances(Cheignon C et al, 2018). They can catalyse the generation of ROS when they attach to Aβ. Furthermore, AD patients' cortex and hippocampus exhibit reduced iron catalytic activity in cytochrome c (hydroxide reductase), It is a part of the energy transduction system in the mitochondria(Benzi G et al, 1995). This leads to an increase in superoxide anions and a decrease in the activity of antioxidant enzymes such as glutathione peroxidase and catalase. The respiratory chain will experience electron leakage due to changes in mitochondrial activity, which will attach to superoxide anions and increase the generation of ROS( da Rosa et al, 2022). Excessive ROS generation can decrease brain plasticity, accelerate aging, and impair the neuronal metabolic cascade response. Since the main source of ROS in cells is the mitochondria, an excessive accumulation of ROS will cause mitochondrial dysfunction and the collapse of mitochondrial homeostasis.(Llanos et al, 2020). Additionally, it has been presented that ROS causes tau hyperphosphorylation and A deposition in the brain during the initial phases of AD.

## II. BIOACTIVE COMPOUNDS FOR ANTI-ALZHEIMER'S ACTIVITIES

### 2.1 Nuts

Age-related behavioural decreases and neuronal function deficits have been identified in the brain. such as a decline in both human and animal motor and cognitive function. The central nervous system (CNS) is particularly vulnerable to oxidative stress and inflammation, both of which worsen with age and are accompanied by a decline in the effectiveness of the body's defence mechanisms against these insults. Polyunsaturated fatty acids are found in nuts.

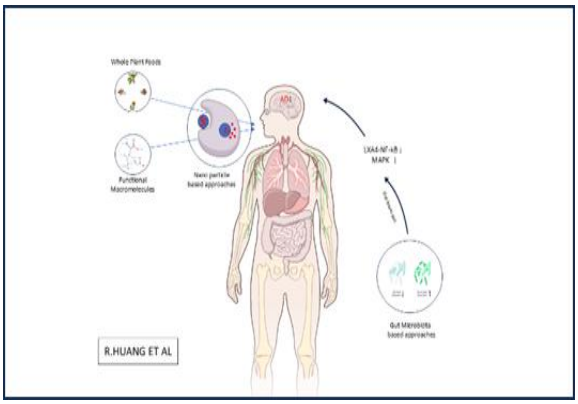



Figure 04 shows how food products/nutraceuticals and Functional Macromolecules exhibit anti-AD activity in humans, and how a healthy gut microbiota blocks the NF-kB and MAPK pathways.

Nuts are recognized to be good providers of oil, protein, and phytosterols, yet each nut has a unique combination and concentration of these nutrients. The fatty acid makeup of the majority of tree nuts varies greatly, though, and as a result, they may have varying health benefits. It should be mentioned that customers occasionally view nuts as fatty foods because they are high in fat and consequently high in energy. Nonetheless, research indicates that including nuts in a diet typically does not result in weight gain and may even aid in weight loss. Additionally, nuts are most well-known and praised for their abundance of unsaturated fat, which is typically regarded as a healthier fat than saturated fat. Nuts' PUFAs have received the greatest attention.

Nuts include alpha-linolenic acid (C18: 3n-3, ALA), an omega-3 fatty acid that serves as a precursor to eicosapentaenoic acid (C20:5n-3, EPA), a long-chain omega-3 fatty acid that is subsequently transformed into docosahexaenoic acid (C22: 6n-3, DHA). The fatty acid chain is further desaturated by adding more double bonds and elongated by adding carbon atoms during the conversion of ALA to EPA and subsequently to DHA.

Omega-3 fatty acids reduce the generation of reactive oxygen species and have anti inflammatory properties. These nuts are rich in phenolic compounds, a type of phytochemicals that are strong antioxidants in vitro. These compounds include flavonoids, anthocyanidins, and phenolic acid. For instance, it has been demonstrated that polyphenols play a role in the reestablishment of calcium homeostasis in the brain's striatal and hippocampus areas, which are essential for basic and secondary memory processes.

Nuts in AD Oxidative stress –

Almonds (*Prunus dulcis)*, family – Rosaceae, are usually found in the Middle East and South Asia ( Especially in Iran, Afghanistan, UAE, and surrounding areas), are a good source of nutrients like vitamin E, arginine, kaempferol, vanillic acid, fibre, etc, and fatty acids like oleic acid. Vanillic acid scavenges reactive oxygen species (ROS), increases the activity of antioxidant enzymes such superoxide dismutase (SOD), catalase, and glutathione peroxidase (GPx), and lessens oxidative damage in neurons. It also suppresses AChE, which helps to maintain the level of acetylcholine, which is crucial for memory. Additionally, it inhibits memory impairments, A beta-induced cytotoxicity, and the buildup of amyloid-beta (Abeta) plaques. Chronic neuroinflammation caused by microglia is linked to AD; pro-inflammatory cytokines such as TNF-alpha, IL-1β, and IL-6 are inhibited by vanillic acid. It reduces inflammation by downregulating the NF-kB pathway.

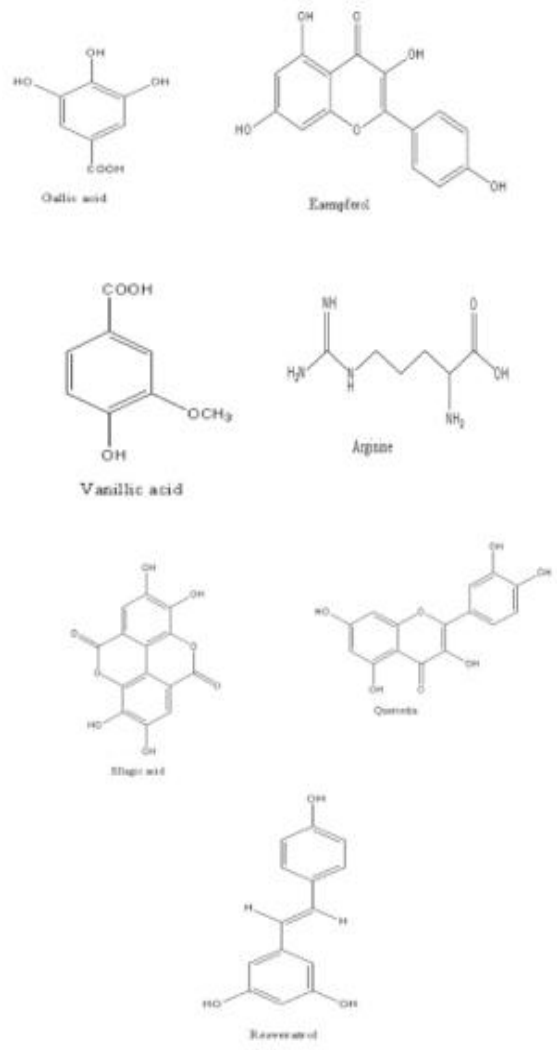
Strong antioxidant kaempferol also has anti-inflammatory properties and inhibits the buildup of A-β plaque. It suppresses the overactive JAK/STAT, NF-kB, and MAPK pathways in AD. It aids in the treatment of AD and maintains cognitive function by activating PI3K/Akt pathways, underregulating BDNF (Brain Derived Neurotrophic Factors), and encouraging the survival, development, and repair of brain neurons.

Walnuts (*Juglans regia),* belonging to the family Juglandaceae, are found in central Asia, the Himalayas, Iran, and regions around the Caspian Sea and the Arabian Peninsula. Walnuts contain nutraceuticals like omega-3 fatty acids (especially ALA), vitamin E, Melatonin, polyphenols (gallic acid, ellagic acids), proteins, fibre, quercetin, and kaempferol. Powerful polyphenols such as gallic acid, quercetin, kaempferol, and ellagic acid function as antioxidants, lowering oxidative stress, a primary cause of AD and neurodegeneration. Deterioration of cognition. Additionally, walnuts protect against damage to healthy neurons by modulating microglial activation and inhibiting inflammatory cytokines in the brain. By altering enzymes such as neprilysin and insulin-degrading enzyme (IDE), it may also promote A-beta clearance. Strong antioxidant polyphenols like gallic acid, quercetin, kaempferol, and ellagic acid reduce oxidative stress, which is a major contributor to AD and neurodegeneration. Cognitive decline. Furthermore, by regulating microglial activity and suppressing inflammatory cytokines in the brain, walnuts prevent harm to healthy neurons. It may also encourage A-beta clearance by changing enzymes like neprilysin and insulin-degrading enzyme (IDE). In addition to polyphenols, quercetin binds to A-beta peptides and stops them from clumping together to form plaques in the brain. It lowers neuroinflammation associated with AD neuronal impairment by suppressing pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-alpha. Cognitive function and synaptic transmission are improved by mild suppression of AChE and BChE (butyrylcholinesterase).

Pistachios (*Pistacia vera),* family Anacardiaceae usually found in central Asia and the Middle East ( Iran, Afghanistan, Turkmenistan). Consumption of pistachios improves and regulates cognition, and it may improve cholesterol levels. It contains nutraceuticals like monounsaturated and polyunsaturated fats, vitamin B6 (pyridoxin), vitamin E, phytosterols, anthocyanins, carotenoids(i.e, Lutein, Zeaxanthin), flavonoids, polyphenols, arginine, and some minerals like magnesium, potassium, etc. Vitamin E, or gamma-tocopherol, is a potent antioxidant that shields the lipid membranes in neurons. Pistachios' lutein, anthocyanins, and polyphenols scavenge reactive oxygen species (ROS), preventing oxidative neuronal damage and delaying cognitive decline. In order to improve cerebral blood flow and brain perfusion—two critical processes for aging brains—arginine raises nitric oxide (NO), which encourages vasodilation. This facilitates the delivery of oxygen and nutrients to neurons. In older individuals, carotenoids such as lutein and zeaxanthin enhance visual memory, speed up processing, and correlate with improved cognitive function.

Groundnuts or peanuts (*Arachis hypogaea)* belonging to Fabaceae (legume family) are mainly founds in India (Gujarat, Tamil Nadu, West Bengal), Africa, China, and other Asian countries. Macro nutrients found in peanuts are protein( 25-30%), dietary fibres, monounsaturated fatty acids, micro nutrients like niacin (vit B3), folate, vit E, Magnesium, phosphorus, potassium, zinc. The main bioactive compound that helps in AD present in peanuts are Resveratrol, isoflavones, coenzyme Q10, arginine, etc. Tau hyperphosphorylation, persistent inflammation, neuronal death, oxidative stress, cognitive loss, and Abeta buildup are all factors in Alzheimer's disease. The chemicals and nutrients included in ground nuts aid in reversing these AD-related processes.

Niacin promotes DNA repair and slows down cognitive ageing. Resveratrol and isoflavones function as antioxidants and prevent the development of A-β plaque. Through nitric oxide, arginine enhances cerebral blood flow, or blood flow in the brain capillaries. Homocysteine, a neurotoxic substance linked to AD, is decreased by folate. Additionally, groundnut resveratrol inhibits Abeta aggregation and promotes Abeta clearance through the activation of proteasome and autophagy mechanisms. Strong antioxidants like coenzyme Q10, vitamin E, and resveratrol shield neurons from oxidative damage, which is a the main factor in the progression of AD. Help maintain mitochondrial function and stop neuronal death.




2.2 VEGETABLES

The abundance of antioxidants, phytoconstituents, vitamins, minerals, and other nutrients found in vegetables makes them protective against AD. Green leafy vegetables (such as spinach, kale, broccoli, etc.) offer lutein, folate, and vitamin K, while cruciferous vegetables (such as Brussels sprouts, broccoli, etc.) contain sulforaphane. Colorful vegetables like tomatoes, carrots, and beetroot are rich in β-carotene and carotinoids, which improve blood flow and lessen mitochondrial dysfunction in the brain. Consuming these kinds of veggies regularly may enhance brain function and prevent the onset of AD. As antioxidants, anti-amyloid, anti-inflammatory, and vascular protective mechanisms, the compounds found in vegetables—beta carotene, zeaxanthin, lycopene, apigenin, quercetin, kaempferol, sulforaphane, allicin, vitamin, ferulic acid, coumaric acid, etc.—help to decrease the progression of AD in the aging brain.

Broccoli (*Brassica oleracea var. italica) is* from the family of Brassicaceae(mustard family). It can be found in the Mediterranean region (Italy) and later spread worldwide. Now grown in China, India, the USA, Spain, etc. Taking broccoli and its compounds has been linked to some health benefits. These effects are often attributed to the abundance of micronutrients and phytochemicals in broccoli (*Maria D et al, 2024*). It is a great source of glucosinolates like sulforaphane, carotenoids like lutein, β-carotene, and flavonoids like quercetin, kaempferol, vitamin C, vitamin K, and folate etc.

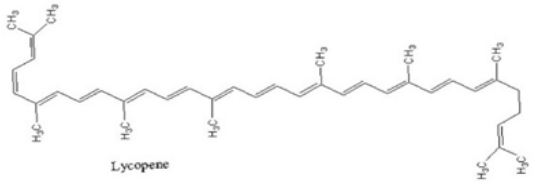
FLAVONOIDS suppress NF-kB signalling and lower neuroinflammation in the brain. Phytoconstituents in broccoli support brain-derived neurotrophic factor (BDNF) signalling, improving memory and learning. Sulforaphane acts by activating the NRF2 pathway, which increases antioxidant enzymes and reduces oxidative stress, which is a major factor in neuronal death in AD, and it also reduces amyloid-beta accumulation and inhibits tau protein hyperphosphorylation. Sulforaphane also suppresses NF-kB signalling. Vit-K and folate from broccoli improve cerebral blood flow and support acetylcholine synthesis, essential for cognition. Regular intake of broccoli as part of a MIND (Mediterranean diet) is linked with slower cognitive decline and better brain health.

One of the most important phytochemicals in the carotenoid group, lycopene has numerous potential uses and health advantages, chief among them being its antioxidative qualities. Lycopene is abundant in tomatoes (Solanum lycopersicum), which are members of the Solanaceae family and are grown in India, China, Italy, the United States, Turkey, and other nations. Additionally, it contains quercetin, lutein, beta-carotene, naringenin, caffeic acid, ferulic acid, folate, vitamins C and E, and more. Lycopene and beta-carotene, two compounds found in tomatoes, operate as antioxidants by preventing lipid peroxidation and reactive oxygen species (ROS) and shielding neuronal membranes from oxidative stress. Additionally, lycopene lowers tau hyperphosphorylation and A-beta aggregation. Additionally, it enhances mitochondrial function and cerebral blood flow, which supports neuronal energy

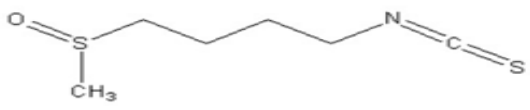
metabolism and preserves memory and cognition. Tomato flavonoids(quercetin, naringenin) suppress NF-kB and pro-inflammatory cytokines, lowering chronic neuroinflammation in the brain.

Rich in lutein, zeaxanthin, folate, vitamin K, and beta-carotene, spinach (Spinacia oleracea), a member of the Amaranthaceae family, is found in India, China, Asian countries, America, and certain European countries. Sphingolipids, which are essential for synaptic function, are regulated by vitamin K. The neuronal membrane is protected by lutein and zeaxanthin, which are potent antioxidants, and folate lowers homocysteine, which further lowers the risk of neurodegeneration. Beta-carotene and luteolin are found in carrots (Daucus carota), which are members of the Apiaceae family. Lutein inhibits microglial activation, which reduces neuroinflammation, while beta-carotene shields neuronal membranes from oxidative stress damage.

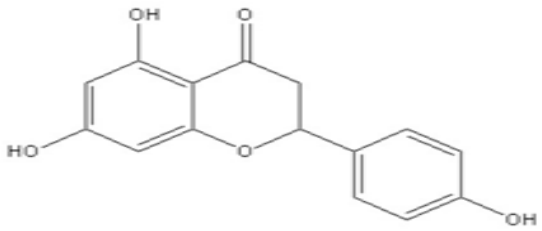
The Amaryllidaceae family includes onions (Allium cepa), which are rich in organosulfur compounds like quercetin that prevent amyloid-beta aggregation and have potent anti-inflammatory and antioxidant properties in the aging brain. Spinach contains organosulfur chemicals that preserve neurons and improve blood circulation. Allicin, the primary phytoconstituent found in garlic (Allium sativum), a member of the Amaryllidaceae family, and S-allyl cysteine support brain health and aid in the management of oxidative stress linked to AD. It enhances memory, learning, and general cognitive health by lowering oxidative stress, neuroinflammation, and the amyloid-beta's ability to cause neuronal damage.



Lycopene



Sulforaphane



Naringenin

2.3 Fruits

Vitamins, fibre, flavonoids, carotenoids, polyphenols, and antioxidants found in abundance in fruits offer neuroprotection by lowering oxidative stress, inflammation, and vascular dysfunction. Fruit-rich nourishments are consistently associated with a lower risk of AD and shorter cognitive deterioration. Because they include polyphenols, flavonoids, vitamins, and carotenoids that work through antioxidant, anti-amyloid, anti-inflammatory, and neuroprotective processes, berries, citrus fruits, pomegranates, apples, grapes, and papaya are especially useful in AD.

The Lythraceae family, which includes the pomegranate (Punica granatum), is found in the Middle East, Central Asia, Mediterranean Europe, America, and North Africa. Pomegranates have been grown for more than 4,000 years throughout the Mediterranean Basin. Punicalagin, ellagic acid, gallic acid, anthocyanins, catechins, tannins, and vitamin C are the main phytochemicals found in it. Phytochemicals are extracted from its seeds, peel, juice, and seed oil. Anthocyanins and punicalagin scavenge free radicals to prevent oxidative damage to the neuronal membrane. It decreases microglial activation and the generation of pro-inflammatory cytokines (IL-6, TNF-alpha), inhibits A-β aggregation, fibril formation, and improves the removal of A-β plaques. It enhances memory and cognition by promoting neurogenesis and synaptic plasticity.

Citrus fruit contains a large number of bioactive compounds, like tangeretin, flavones, nobiletin, naringin, hesperidin, narirutin, etc. Citrus Polymethoxylated flavones(PMFs) have beneficial effects on cognitive function. They work by modifying pathogenic characteristics such neuroinflammation, oxidative stress, A-beta/tau pathology, and enhancing synaptic plasticity.

Lemon(Citrus limon) belongs to the family Rutaceae and contains compounds like Hesperidin, diosmin,

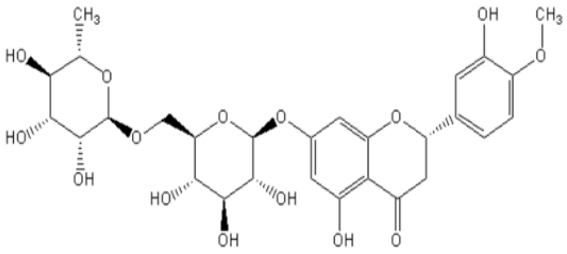
eriocitrin, ferulic acid, caffeic acid, Vitamin C, limonene, and other terpenoids and coumarins, which scavange reactive oxygen species (ROS), reduce lipid peroxidation in neurons, and prevent oxidative stress-induced neurodegeneration. Some lemon peel extract inhibits AChE and BChE, increasing ACh availability in the brain and improving memory and cognition. They also suppress neuroinflammation by downregulating TNF-alpha, IL-1beta, NF-kB signalling pathways, and prevent mitochondrial dysfunction in neurons, thereby reducing apoptosis. Limonene & Hesperidin reduce microglial activation.

Grapes(Vitis vinifera) belong to the family Vitaceae, rich in resveratrol, proanthocyanidins, quercetin, catechin, anthocyanins, Vitamins, etc, which are strongly neuroprotective in Alzheimer's. Some berries like Blueberry(Vaccinium corymbosum), Strawberry(Fragaria ananassa), Blackberry(Rubus fruticosus), Mulberry(Morus alba) contain polyphenols, flavonoids, phenolic acids, resveratrol, vitamin C & E, etc. Like other citrus fruits, they act as antioxidant, anti-amyloid, and anti-inflammatory agents and increase BDNF, improving signalling and hippocampus and overall mental health.

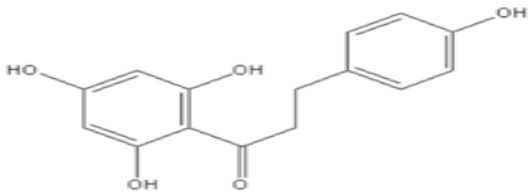
Apple(Malus domestica), belonging to the family Rosaceae, found in Central Asia, Turkey, Poland, India, Kazakhstan, etc, is rich in quercetin, catechin, epicatechin, chlorogenic acid, phloridzin, phloretin, and vitamin C. Chlorogenic acid reduces oxidative stress, modulates glucose metabolism. Phlorizin and phloretin are neuroprotective polyphenols unique to apples. Apple juice concentrate has been shown to increase acetylcholine production and neurogenesis in the hippocampus and prevent mitochondrial dysfunction, preserving energy metabolism in neurons.

Banana (Musa spp.) belongs to the family Musaceae is originated in India, Malaysia, China, Papua New Guinea, and other Asian countries, Africa, Europe, and America, Brazil, etc. Banana contains dopamine & catecholamines, pyridoxine, Phenolic compounds, and some minerals like potassium, magnesium, which acts as a strong antioxidant. Pyridoxine (Vitamin B6), acetylcholine, and dopamine pathways, critical in memory, banana peel extracts show acetylcholinesterase inhibitory activity, increasing acetylcholine levels.

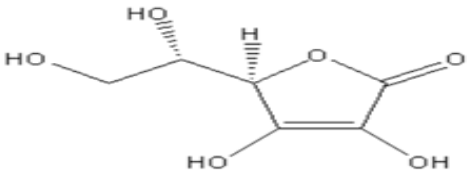
Avocado (Persea americana), belonging to the family Lauraceae, is found in Central America, Mexico, the Dominican Republic, Peru, Colombia, Kenya, etc. It is a great source of lutein(xanthophyll carotenoid), MUFAs, Vitamin C, E & B6, phytosterols, phenolics, and folate. Lutein enhances memory and executive function, protects against oxidative stress in the hippocampus, and MUFAs improve membrane fluidity, essential for neurotransmission. Vitamin E protects against lipid peroxidation and beta-amyloid toxicity, improves cerebral perfusion, and reduces vascular risk factors. Polyphenolic compounds also increase synaptic plasticity, which gives cognitive support.



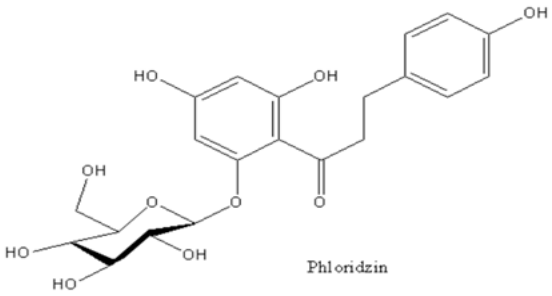
Hesperidin



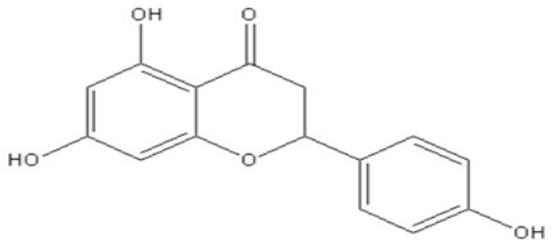
Phloretin



Vitamin C



Phloridzin



Naringenin

1.4 Seeds –

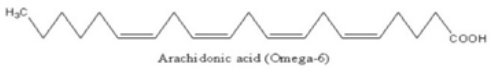
2.4 Seeds

Due to their abundance of bioactive compounds that may aid in protecting the brain and slowing neurodegeneration, seeds are becoming more and more popular in AD. Because they contain antioxidants, omega-3 fatty acids, vitamins, lignans, and essential minerals that together protect neurons, lower oxidative stress, and enhance memory and cognitive function, seeds such as chia, flax, sesame, pumpkin, and sunflower seeds are crucial for the prevention and treatment of AD.

The moong bean (*Vigna radiata*), a member of the legume family Fabaceae, originates from India and Southeast Asia. These include bioactive phytoconstituents such as flavonoids, phenolic compounds, proteins, peptides, vitamins, minerals, and polyphenols (vitexin, isovitexin, gallic acids, and catechins). Free radicals are scavenged by vitexin and isovitexin, which also lessen oxidative stress, which is a crucial factor in the development of β plaque and neuronal damage. Moong bean extract reduces pro-inflammatory cytokines (TNF-alpha, IL-1β) that exacerbate AD pathogenesis by suppressing neuro-inflammatory responses. Vitexin is very effective at treating conditions affecting the central nervous system, such as ischemic stroke, AD, and PD. In a number of cell lines, it lessens apoptosis and neuronal death brought on by A-β. By increasing the expression of NRF2 and hem oxygenase 1, vitexin pretreatment improves intracellular antioxidant defences by reducing A-$\beta_{25-35}$ induced ROS/RNS (reactive oxygen/nitrogen species) production, lipid peroxidation, protein oxidation, and mitochondrial dysfunction in neuro-2a cells (Xu et al. 2021).

Flavonoids, tannins, and phenolic compounds are abundant in moong beans. The hydroxy benzoic acid (gallic, protocatechuic, syringic, gentilics, and vanillic acid) and hydroxy cinnamic acids (P-coumaric phenolic cinnamic caffeic acid) and caffeoylquinic acid isomer (chlorogenic acid) can be produced from 19 distinct types of primary phenolic chemicals. Hot flashes and constipation are alleviated by green moong beans. It prevents osteoporosis, protects the heart, and controls blood sugar and cholesterol levels. Additionally, it has anti-inflammatory, anti-oxidant, antibacterial, immunity-boosting, anti-obesity, and anti-cancer properties (Kaura et al, 2016).

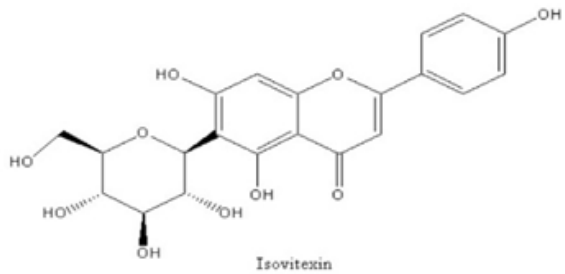
Originally from Central America, Mexico, Europe, Asia, and Africa, pumpkin seeds (Cucurbita pepo), which are now also found in India, Ukraine, and the United States, are a member of the Cucurbitaceae family. PUFAs (omega-3, omega-6 fatty acids), phytosterols, polyphenols, tryptophan, carotenoids, vitamins, and minerals are the primary components of pumpkin seeds. Rich in carotenoids, polyphenols, and vitamin E, it lowers oxidative stress and neutralizes ROS. Tryptophan (a precursor to serotonin and melatonin) and choline, which are found in pumpkin seeds, may counteract the cholinergic deficiency in AD and enhance acetylcholine transmission. Tryptophan promotes the melatonin pathway and serotonin synthesis, which promote mood and sleep. Sleep difficulties are a sign of AD progression. Additionally, the polyphenol has anti-amyloidogenic properties that shield neurons from the cytotoxicity caused by amyloid. Zinc may help with memory and synaptic plasticity.



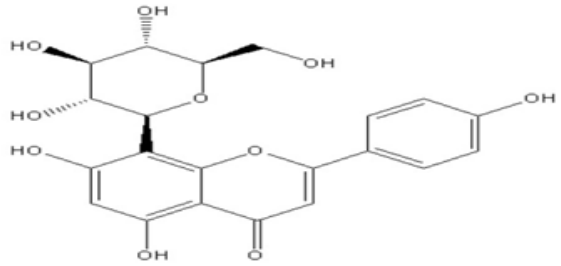
Arachidonic acid (Omega-6)

Eicosapentaenoic acid, EPA(Omega-3)

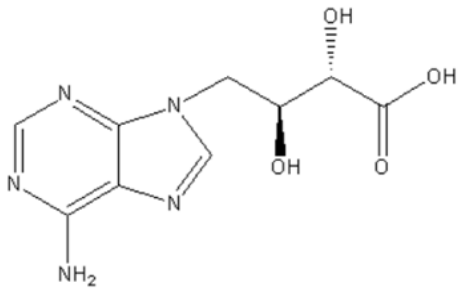
Docosahexaenoic acid,DHA (Omega-3)



Isovitexin



Vitexin

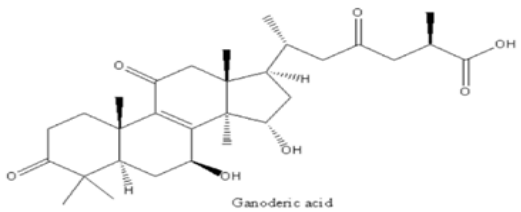


Eritadenine

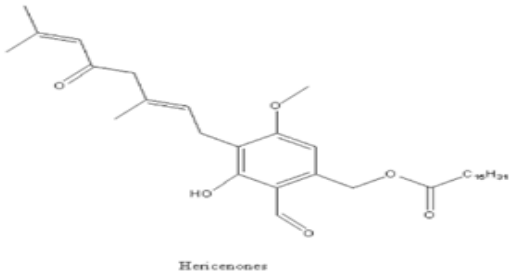
3 Mushrooms

Different types of mushrooms have some potential pharmacologically active ingredients which have neuroprotective activities and plays the lead role in Alzheimer's disease management. Many edible and medicinal mushrooms include bioactive compounds with neuroprotective qualities, including terpenoids, polysaccharides, phenolics, and ergothioneine. It has been demonstrated that mushroom extracts, especially those from Hericium erinaceus and Ganoderma lucidum, offer cognitive and neuroprotective benefits. A few promising small-scale research have shown that supplementing with mushrooms improves memory function and moderate cognitive impairment (MCI).

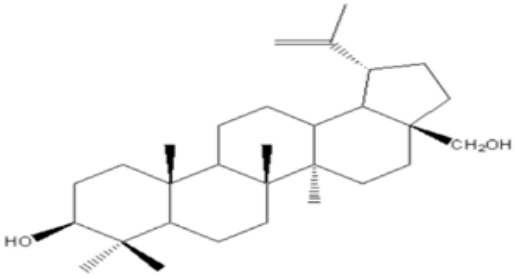
The mostly used mushrooms in AD are Reish (*Ganoderma lucidum*), Lion's Mane (*Hericium erinaceus*), Cordyceps(*Cordyceps militaris/sinensis*), Chaga(*Inonotus obliquus*), Shiitake(*Lentinula edodes*), Maitake(*Grifola frondosa*), Agaricus blazei, Turkey Tail(*Trametes versicolor*), Enokitake(*Flammulina velutipes*), Oyster mushroom(*Pleurotus ostreatus*). Mainly found phytoconstituents from these mushrooms are natural polysaccharides, triterpenoids, ganoderic acid, erinacines, hericenones, cordycepin, adenosine, betulin, polyphenols, melanin, lentinan, eritadenine, beta-glucans, ergosterol, polysaccharide-K, ergothioneine etc. these works by inhibiting Aβ-induced neurotoxicity, reduces ROS, and improves ,mitochondrial function. They also stimulates nerve growth factor(NGF), protects neurons from apoptosis, inflammation, and oxidative damage. They are strong antioxidant which reduces lipid peroxidation in brain neuronal cells. The phytoconstituents present in those mushrooms improves cognitive function and helps in oxidative stress management in brain and protects them from mitochondrial dysfunction. They inhibit microglial activation and cytokine release.



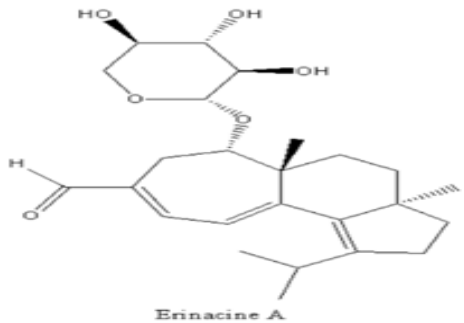
Ganoderic acid



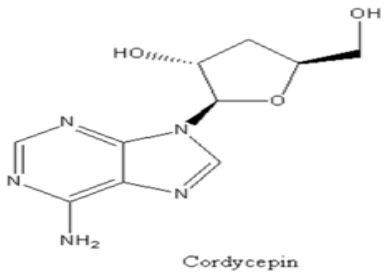
Hericenones



Betulin



Erinacine A



Cordycepin

Tables Nuts

| Nuts | Key Compounds | Mechanism of Action | References |
|---|---|---|---|
| Walnuts *(Juglans regia)* | Polyphenols, ellagic acid, omega-3 fatty acids | Antioxidant activity, reduces ROS, improves synaptic plasticity, prevents Aβ aggregation | Poulose SM et al. *Alzheimers Dis.* 2012;28(3):611–622. |
| Almonds (Prunus dulcis) | Vitamin E (α-tocopherol), flavonoids, phenolic acids | Reduces lipid peroxidation, enhances antioxidant enzymes (SOD, GPx), improves memory | Barbalho SM et al. *Nutrients.* 2022;14(14):2953. |
| Pistachios (Pistacia vera) | Lutein, γ-tocopherol, polyphenols | Scavenges ROS, improves endothelial and mitochondrial function, neuroprotective | Sari F et al. *Nutrients.* 2010;2(7):710–718. |
| Hazelnuts (Corylus avellana) | Vitamin E, proanthocyanidins, phenolics | Protects neuronal membranes, reduces oxidative DNA damage | Alasalvar C et al. *Eur J Nutr.* 2010;49(6):419–428. |
| Cashews (Anacardium occidentale) | Polyphenols, anacardic acids, selenium, magnesium | Antioxidant effect, reduces oxidative stress, supports neuronal survival | Ogunwolu SO et al. *Afr J Biotechnol.* 2010;9(21):3218–3223 |
| Brazil Nuts (Bertholletia excelsa) | Selenium, vitamin E, phenolics | Boosts glutathione peroxidase, decreases ROS, reduces neuroinflammation | Cardoso BR et al. *Nutrients.* 2017;9(7):681. |
| Pecans (Carya illinoinensis) | Flavonoids, ellagic acid, vitamin E | Antioxidant capacity, decreases lipid peroxidation and improves cognitive function | Hudthagosol C et al. *J Nutr Neurosci.* 2011;14(6):253–262. |

Vegetables

| Vegetable | Key Compounds | Mechanism of Action | References |
|---|---|---|---|
| Spinach (Spinacia oleracea) | Lutein, β-carotene, vitamin C, vitamin E, flavonoids | Scavenges ROS, enhances antioxidant enzyme activity, reduces lipid peroxidation | Johnson EJ. Nutrients. 2014;6(10):4472–4491. |
| Broccoli (Brassica oleracea var. italica) | Sulforaphane, vitamin C, quercetin, kaempferol | Activates Nrf2 pathway, boosts glutathione levels, protects mitochondria | Tarozzi et al. Oxid Med Cell Longev. 2013;2013:946491. |
| Tomato (Solanum lycopersicum) | Lycopene, vitamin C, phenolic acids | Reduces ROS, inhibits Aβ aggregation, protects against neuronal apoptosis | Sachdeva AK, Chopra K. Eur Neuropsychopharmacol. 2015;25(10):1783–1791. |

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|---|---|---|---|
| Carrot (Daucus carota) | β-carotene, luteolin, phenolics | Prevents ROS-induced neuronal damage, modulates cholinergic activity | Rinaldi P et al. Neurobiol Aging. 2003;24(5):717–723. |
| Onion (Allium cepa) | Quercetin, sulfur compounds | Strong antioxidant & anti-inflammatory, reduces neuronal apoptosis | Ishige K et al. Free Radic Biol Med. 2001;30(4):433–446. |
| Garlic (Allium sativum) | S-allyl cysteine, allicin, flavonoids | Scavenges free radicals, inhibits Aβ neurotoxicity, improves mitochondrial function | Chauhan NB. J Nutr Biochem. 2006;17(9):595–602. |
| Kale (Brassica oleracea var. sabellica) | Lutein, zeaxanthin, flavonoids | Neutralizes free radicals, reduces neuroinflammation | Johnson EJ et al. J Acad Nutr Diet. 2013;113(11):1448–1456. |
| Beetroot (Beta vulgaris) | Betalains, nitrates, phenolics | Enhances cerebral blood flow, reduces oxidative stress, protects neurons | Wootton-Beard PC, Ryan L. Nutrients. 2011;3(3):313–328. |
| Sweet Potato (Ipomoea batatas) | β-carotene, anthocyanins, vitamin C | Antioxidant effect, decreases lipid peroxidation, supports neuronal survival | Islam MS. Food Res Int. 2006;39(2):143–153. |
| Cabbage (Brassica oleracea var. capitata) | Indole-3-carbinol, vitamin C, anthocyanins | Induces phase II detoxifying enzymes, reduces oxidative DNA damage | Higdon et al. Pharmacol Res. 2007;55(3):224–236. |

Fruits

| Fruit | Key Compounds | Mechanism of Action | References |
|---|---|---|---|
| Blueberries (Vaccinium corymbosum) | Anthocyanins, flavonoids, vitamin C | Strong antioxidant, reduces ROS, protects neurons, improves memory and cognitive function | Joseph JA et al. *J Neurosci.* 1999;19(18):8114–8121. |
| Strawberries (Fragaria × ananassa) | Ellagic acid, anthocyanins, flavonoids | Scavenges free radicals, reduces lipid peroxidation, improves neuronal signaling | Shukitt-Hale B et al. *Nutr Neurosci.* 2008;11(3):89–97. |
| Grapes (Vitis vinifera) | Resveratrol, flavonoids, proanthocyanidins | Antioxidant, inhibits Aβ aggregation, reduces neuroinflammation | Wang J et al. *J Nutr Biochem.* 2008;19(6):357–367. |
| Pomegranate (Punica granatum) | Polyphenols (ellagitannins, punicalagin), anthocyanins | Reduces ROS, decreases oxidative stress markers, protects synapses | Hartman RE et al. *Neurobiol Dis.* 2006;24(3):506–515. |
| Apples (Malus domestica) | Quercetin, catechins, vitamin C | Antioxidant, inhibits lipid peroxidation, protects neurons from oxidative damage | Boyer J, Liu RH. *Nutr J.* 2004;3:5. |
| Oranges (Citrus sinensis) | Vitamin C, hesperidin, flavonoids | Scavenges ROS, reduces neuroinflammation, improves mitochondrial function | Spencer JP et al. *Free Radic Biol Med.* 2000;29(9):1021–1030. |
| Cherries (Prunus avium) | Anthocyanins, quercetin, vitamin C | Protects neurons from oxidative stress, reduces lipid peroxidation, improves cognitive function | Seymour EM et al. *J Nutr Biochem.* 2007;18(7):450–460. |

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|---|---|---|---|
| Kiwi (Actinidia deliciosa) | Vitamin C, carotenoids, flavonoids | Strong antioxidant, reduces ROS, protects synaptic integrity | Shi J et al. *Food Chem.* 2008;106(3):991–996. |
| Mango (Mangifera indica) | Mangiferin, carotenoids, polyphenols | Antioxidant, anti-inflammatory, protects neurons from oxidative damage | Subash S et al. *Phytother Res.* 2014;28(3):404–412. |
| Guava (Psidium guajava) | Vitamin C, lycopene, flavonoids | Reduces ROS, supports antioxidant enzymes, protects against neuronal apoptosis | Joshi S et al. *Food Sci Technol.* 2016;53(1):451–459. |

Seeds

| Seeds / Legumes | Key Compounds | Mechanism of Action | References |
|---|---|---|---|
| Soybeans (Glycine max) | Isoflavones (genistein, daidzein), lecithin, saponins | Antioxidant, reduces ROS, modulates estrogen receptors, decreases Aβ toxicity | Bagheri M et al. Nutr Neurosci. 2011;14(4):183–188. |
| Black Beans (Phaseolus vulgaris) | Anthocyanins, polyphenols, folate | Scavenges free radicals, improves mitochondrial function, reduces lipid peroxidation | Xu B, Chang SK. J Agric Food Chem. 2010;58(23):12254–12264. |
| Lentils (Lens culinaris) | Polyphenols, flavonoids, vitamin B complex | Enhances antioxidant enzyme activity, reduces oxidative DNA damage | Dueñas M et al. Food Chem. 2016;196:703–711. |
| Chickpeas (Cicer arietinum) | Polyphenols, flavonoids, saponins | Inhibits ROS, protects neurons, improves cholinergic activity | Jukanti AK et al. Br J Nutr. 2012;108(S1):S11–S26. |
| Peanuts (Arachis hypogaea) | Resveratrol, p-coumaric acid, flavonoids | Antioxidant, anti-inflammatory, improves synaptic plasticity | Kopp P. Eur J Clin Nutr. 1998;52(3):169–173. |
| Sesame Seeds (Sesamum indicum) | Sesamol, sesamin, lignans, vitamin E | Strong antioxidant, reduces lipid peroxidation, improves neuronal survival | Kang MH et al. Clin Chim Acta. 1998;270(2):179–188. |
| Flaxseeds (Linum usitatissimum) | Alpha-linolenic acid (ALA), lignans, phenolics | Improves mitochondrial function, reduces ROS, supports neuronal membrane integrity | Cunnane SC et al. Nutr Neurosci. 2012;15(3):128–134. |
| Sunflower Seeds (Helianthus annuus) | Vitamin E, selenium, phenolic acids | Protects neuronal lipids from peroxidation, enhances antioxidant enzyme activity | Jiang Q. Free Radic Biol Med. 2014;72:76–90. |
| Pumpkin Seeds (Cucurbita pepo) | Zinc, carotenoids, vitamin E, polyphenols | Antioxidant and neuroprotective, improves learning and memory in AD models | Zanwar AA et al. Pharmacogn Rev. 2014;8(16):116–123. |
| Walnuts (Juglans regia) | Polyphenols, vitamin E, omega-3 fatty acids | Reduces ROS, improves cognitive function, prevents Aβ aggregation | Poulose SM et al. J Alzheimers Dis. 2012;28(3):611–622. |

Marine Products

| Marine Product | Key Compounds | Mechanism of Action | References |
|---|---|---|---|
| Salmon, Sardine, Mackerel (Fatty Fish) | vitamin D, Omega-3 fatty acids (DHA, EPA) | Reduces ROS production, improves mitochondrial function, decreases Aβ aggregation, anti-inflammatory effects | Cunnane SC et al. Nat Rev Neurosci. 2009;10(12):791–802. |
| Seaweed (Brown algae – Laminaria, Undaria, Ecklonia) | Fucoxanthin, phlorotannins, fucoidan | Potent antioxidant, scavenges ROS, reduces neuroinflammation, inhibits Aβ-induced neurotoxicity | Fernando IS et al. Mar Drugs. 2017;15(12):393. |
| Red Algae (Porphyra, Palmaria) | Astaxanthin, phycoerythrin, sulfated polysaccharides | Strong antioxidant, protects neuronal membranes, prevents lipid peroxidation, improves cognition | Grimmig B et al. J Alzheimers Dis. 2017;55(2):459–474. |
| Green Algae (Chlorella, Ulva) | Chlorophyll, carotenoids, polyphenols | Enhances antioxidant enzyme activity (SOD, CAT, GPx), reduces oxidative DNA damage | Kang C et al. Nutrients. 2021;13(4):1231. |
| Spirulina (Cyanobacteria) | Phycocyanin, β-carotene, polyunsaturated fatty acids | Inhibits ROS, reduces neuronal apoptosis, enhances mitochondrial function | Wu Q et al. Oxid Med Cell Longev. 2016;2016:6905453. |
| Marine Mollusks (Oysters, Mussels, Clams) | Taurine, zinc, selenium, omega-3 fatty acids | Reduces oxidative stress, protects synaptic plasticity, supports antioxidant enzymes | Manczak M et al. Hum Mol Genet. 2010;19(20):3959–3972. |
| Sea Cucumber (Holothuria species) | Triterpene glycosides, sulfated polysaccharides | Antioxidant and anti-inflammatory activity, protects neurons against oxidative damage | Pangestuti R, Arifin Z. Mar Drugs. 2018;16(12):477. |
| Krill Oil | Phospholipid-bound DHA/EPA, astaxanthin | Improves membrane integrity, reduces ROS, prevents mitochondrial dysfunction | Ulven SM, Holven KB. Nutrients. 2015;7(6):3648–3667. |
| Shrimp & Lobster Shell Extracts | Astaxanthin, chitosan | Astaxanthin reduces oxidative stress and neuroinflammation; chitosan provides neuroprotection | Fakhri S et al. J Funct Foods. 2018;48:111–125. |

Mushroom

| Mushroom | Key Compounds | Mechanism of Action | References |
|---|---|---|---|
| Reishi (Ganoderma lucidum) | Polysaccharides, triterpenoids, ganoderic acids | Antioxidant, reduces ROS, inhibits Aβ-induced neurotoxicity, improves mitochondrial function | Pan Y et al. *Int J Mol Sci.* 2015;16(6):14708–14725. |
| Lion's Mane (Hericium erinaceus) | Erinacines, hericenones, polysaccharides | Stimulates nerve growth factor (NGF), reduces oxidative stress, promotes neuronal survival | Mori K et al. *Biomed Res.* 2009;30(4):169–175. |
| Cordyceps (Cordyceps militaris / sinensis) | Cordycepin, polysaccharides, adenosine | Scavenges ROS, enhances antioxidant enzyme activity, protects neurons from apoptosis | Paterson RR. *Phytochem Rev.* 2008;7:175–185. |

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|---|---|---|---|
| Chaga (Inonotus obliquus) | Betulin, polyphenols, melanin | Strong antioxidant, reduces lipid peroxidation, protects against Aβ neurotoxicity | Kim YO et al. *Food Chem Toxicol.* 2006;44(12):1973–1980. |
| Shiitake (Lentinula edodes) | Lentinan, eritadenine, polysaccharides | Enhances antioxidant defense, reduces oxidative stress markers, supports neuronal health | Kidd PM. *Altern Med Rev.* 2000;5(1):64–74. |
| Maitake (Grifola frondosa) | Beta-glucans, polysaccharides | Antioxidant, improves mitochondrial function, modulates neuroinflammation | Kidd PM. *Altern Med Rev.* 2000;5(1):64–74. |
| Agaricus blazei | Beta-glucans, ergosterol, phenolics | Reduces ROS, protects neurons, anti-inflammatory, supports cognitive function | Wasser SP. *Int J Med Mushrooms.* 2002;4(1):31–62. |
| Turkey Tail (Trametes versicolor) | Polysaccharide-K (PSK), polysaccharopeptides | Enhances antioxidant enzymes, reduces oxidative damage in neurons | Heleno SA et al. *Food Funct.* 2015;6(3):739–757. |
| Enokitake (Flammulina velutipes) | Ergothioneine, polysaccharides, phenolics | Potent antioxidant, protects neurons from oxidative stress, improves cognitive function | Kalaras MD et al. *Nutrients.* 2017;9(6):536. |
| Oyster Mushroom (Pleurotus ostreatus) | Lovastatin, ergothioneine, polysaccharides | Reduces ROS, protects neuronal mitochondria, enhances antioxidant defense | Muszyńska B et al. *Molecules.* 2018;23(2):377. |

## III. CONCLUSION

As the population ages, AD has emerged as a pressing social and public health concern that significantly burdens both individuals and society. Numerous studies have put up several theories regarding the cause and clinical condition of AD, offering useful data for treating AD with several targets. Regretfully, anti-AD medications used in clinical settings today can only postpone symptoms; they cannot cure AD. The connection between AD and neuroinflammation may offer a fresh approach to the search for and creation of new AD treatment drugs. Alkaloids, steroids, terpenoids, flavonoids, and polyphenols are examples of anti-inflammatory natural products that have the potential to prevent and alleviate AD symptoms, given that natural products generally have many desirable qualities for drug discovery and development, such as being readily available, diversely bioactive, less toxic, and easily modified. However, in order to produce anti-AD medications, considerable work on medicinal chemistry centred on natural compounds that combat neuroinflammation is anticipated.

Appendix –
AD – Alzheimer's disease
FDA- Food and Drug Administration
Ach- Acetylcholine
AChE- Acetylcholinesterase
BChE- Butyrylcholinesterase
ROS- Reactive Oxygen Species
ALA- Alpha-linolenic Acid
EPA- Eicosapentaenoic Acid
DHA- Docosahexaenoic Acid
SOD- Superoxide Dismutase
GPx- Glutathione Peroxidase
MAPK- Mitogen-Activated Protein Kinase
NF-kB- nuclear factor kappa-light-chain-enhancer of activated B cells.
BDNF- Brain-Derived Neuropathic Factor
IDE- Insulin-degrading Enzyme
RNS- Reactive Nitrogen Species

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