

Review

The Potential Mechanism and the Role of Antioxidants in Mitigating Oxidative Stress in Alzheimer's Disease

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Abstract

Alzheimer's disease (AD) is the most prevalent cause of dementia and a significant contributor to health issues and mortality among older individuals. This condition involves a progressive deterioration in cognitive function and the onset of dementia. Recent advancements suggest that the development of AD is more intricate than its underlying brain abnormalities alone. In addition, Alzheimer's disease, metabolic syndrome, and oxidative stress are all intricately linked to one another. Increased concentrations of circulating lipids and disturbances in glucose homeostasis contribute to the intensification of lipid oxidation, leading to a gradual depletion of the body's antioxidant defenses. This heightened oxidative metabolism adversely impacts cell integrity, resulting in neuronal damage. Pathways commonly acknowledged as contributors to AD pathogenesis include alterations in synaptic plasticity, disorganization of neurons, and cell death. Abnormal metabolism of some membrane proteins is thought to cause the creation of amyloid (A β) oligomers, which are extremely hazardous to neurotransmission pathways, especially those involving acetylcholine. The interaction between A β oligomers and these neurotransmitter systems is thought to induce cellular dysfunction, an imbalance in neurotransmitter signaling, and, ultimately, the manifestation of neurological symptoms. Antioxidants have a significant impact on human health since they may improve the aging process by combating free radicals. Neurodegenerative diseases are currently incurable; however, they may be effectively managed. An appealing alternative is the utilization of natural antioxidants, such as polyphenols, through diet or dietary supplements, which offer numerous advantages. Within this framework, we have extensively examined the importance of oxidative stress in the advancement of Alzheimer's disease, as well as the potential influence of antioxidants in mitigating its effects.

Keywords: Alzheimer's disease; amyloid-beta; amyloid plaques; reactive oxygen species; antioxidants; tau protein



1. Introduction

The unique histopathologic abnormalities known as tangles and plaques in the brain of a young persons with mental retardation were first described by Alois Alzheimer around the start of the 20th century. Impaired cognitive skills, including memory problems in the elderly, have been identified as aging symptoms and are hence referred to as “senile dementia”, a disorder whose frequency and incidence increase exponentially with population aging. Alzheimer’s disease (AD) is currently recognized as the prevailing class of dementia, therefore rendering it a matter of significant public health importance [1]. Alzheimer’s disease (AD) is the most common form of dementia, predominantly affecting the older population and is associated with various health complications and increased death rates. The pursuit of a natural intervention to modify the progression of this disease is of significant interest, given its irreversible nature and profound detrimental effects on individuals affected by it [2]. AD is a neurological condition that impairs cognitive abilities. It is brought on by extracellular amyloid beta buildup that manifests as senile plaques and neurofibrillary tangles. The two types of Alzheimer’s disease that are presently identified are early-onset Alzheimer’s disease (EOAD) and late-onset Alzheimer’s disease (LOAD) [3]. People under 65 who do not have senile dementia are impacted by EOAD. A considerably more prevalent variation of AD is LOAD. Patients over 65 with known comorbidities often experience it. Individuals who have encountered depression exhibit a twofold increased likelihood of getting dementia and Alzheimer’s disease (AD) in comparison to those who have not experienced depression. The malfunction of specific neurotransmitter systems is implicated in the occurrence of neurodegenerative changes [4]. Early signs of AD already show abnormalities in the serotonin pathway. There is growing scientific evidence linking dementia and Alzheimer’s disease (AD), and up to 50% of AD patients may have symptoms of depression. Based on epidemiological research, the presence of depression has the potential to serve as a predictive factor for Alzheimer’s disease (AD) and this assertion is substantiated by a meta-analysis, which revealed that patients who experience concurrent depression have earlier onset ages for Alzheimer’s disease. Additionally, because of the increased production of comparable pro-inflammatory cytokines, depression and AD both contribute to inflammation in the central nervous system [5]. Currently, this pathogenicity impacts around 44 million persons globally. The prevalence of neurodegenerative diseases (NDs) and their associated pathological conditions is a significant concern within the current healthcare system. For international scientists, AD represents one of the most difficult pathological frameworks because of its complexity. Alzheimer’s disease (AD) is the most common kind of dementia seen in older adults, accounting for around 60 to 80 percent of all documented cases [6]. It’s vital to note

that increasing losses of neurons, brain activity, and cognitive abilities are hallmarks of AD. An array of risk elements, which includes obesity, diabetes, high blood pressure, air pollution, smoking and hypercholesterolemia, exert a substantial impact on the progression of Alzheimer’s disease (AD) and the design of approaches for preventive measures against this ailment [7]. Nutritional components and physical activity have been demonstrated to be effective variables that aid in its prevention. The amyloid-beta cascade theory, the tau protein hypothesis, the cholinergic hypothesis, and the oxidative hypothesis are all notable hypotheses on Alzheimer’s disease. These hypotheses may provide light on the underlying causes of the illness. Oxidative stress is a shared element in the development of neurodegenerative diseases (NDs) such as Alzheimer’s disease (AD), Parkinson’s disease, Huntington’s disease, amyotrophic lateral sclerosis, and multiple sclerosis [8].

2. Alzheimer’s Disease and the Population Prevalence

The onset of Alzheimer’s disease results in a significant decline in cognitive functioning, which has a significant negative impact on social and vocational activities. This is one of the most significant pathological burdens on individuals. Over 46 million individuals worldwide suffer from dementia, costing an estimated 818 billion in US dollars in 2015 and projected to reach 1 trillion dollars in 2018. The World Health Organisation has prioritised public health in light of the substantial economic and societal costs associated with Alzheimer’s disease [9]. The appearance of extracellular amyloid-beta ($A\beta$) plaques, intraneuronal neurofibrillary tangles predominantly made of hyperphosphorylated tau, brain atrophy, and elevated brain neuroinflammation are the key pathological markers of AD [10]. The idea of amyloid deposits is a generally acknowledged theory for the fundamental causes of AD. According to this hypothesis, Ab dyshomeostasis is implicated in the disease’s cognitive phenotype and is supposed to have a vital role in the reported molecular and cellular changes associated with AD [11]. The formation of the $A\beta$ peptide is achieved by a progressive cleavage process of the amyloid precursor protein (APP), initially mediated by beta-site APP-cleaving enzyme 1 (BACE-1), sometimes referred to as beta-secretase, and subsequently by the gamma-secretase complex [12]. The gamma-secretase complex, which also modulates the notch pathway, is composed of four subunits: presenilin (either 1 or 2), nicastrin, anterior pharynx-defective 1 (APH-1), and presenilin enhancer 2 (PEN2). Among these subunits, presenilin is of primary interest in research and is strongly associated with Alzheimer’s disease due to its role as the catalytic component of the complex. The $A\beta$ peptides resulting from abnormal cleavage of APP, particularly the longer variants, exert detrimental effects on the brain’s cellular environment. These $A\beta$ species exhibit various toxic-

ity profiles, with soluble forms being more neurotoxic compared to the fibrillary (aggregated) forms. Specifically, the soluble Ab1-42 oligomeric form is believed to pose an extremely high risk [13].

Numerous research studies have demonstrated that astrocytes influence the intercellular connection between glial cells and neurons, as well as between glial cells and blood vessels, hence contributing to the deterioration of cellular and functional characteristics associated with Alzheimer's disease (AD) [14,15]. Astrocytes are crucial resident cells within the central nervous system (CNS) involved in several physiological functions. Astrocytes, like neurons, are a diverse group of cells that display many physical and functional characteristics [14,15]. AD is distinguished by several notable attributes, like creation, aggregation and accumulation of A β , as well as disturbances in acetylcholinesterase (AChE) function, imbalances in metal concentrations, oxidative stress brought on by metals, neuroinflammation and numerous other pathological conditions [16]. AD presents a multifaceted profile characterized by various pathological manifestations such as the abnormal accumulation of A β , the demise of cholinergic neurons, the accumulation of microtubule proteins, disturbances in the regulation of oxidative stress caused by metals and several other factors. The etiology of this complex condition remains unidentified [17]. A loss of cell connections and an accumulation of two aberrant protein aggregates, amyloid plaques and neurofibrillary tangles (NFTs), are seen in certain areas of the brain in AD patients. Neurofibrillary tangles (NFTs) and amyloid plaques both accompany the normal aging process, however in AD patients, these two neuropathological indicators are present in unusually high concentrations [18]. The neurofibrillary tangles that are seen in Alzheimer's disease are mostly made up of tau protein.

2.1 Alzheimer's Disease Pathogenesis

The original source of the amyloid plaques is the amyloid precursor protein (APP). The alpha-, beta-, and gamma secretase enzymes are in charge of cleaving APP. The non-harmful pathway involves the enzymatic decomposition of the APP by alpha- and gamma-secretase at critical junctures, which favor the generation of soluble APP and limit the formation of toxic Ab by beta-secretase [19]. The pathogenic pathway involves the enzyme beta-secretase (BACE-1), which initiates the cleavage of the amyloid precursor protein (APP) molecule at the N-terminus of the A chain. The primary secretase involved in the metabolism of APP is BACE-1, an aspartyl protease embedded in the cell membrane. Secrease then digests the last piece of APP that is attached to the neuronal cell membrane [20]. Further cleavages result in the liberation of A β , which is then released into the extracellular surroundings. Subsequently, it forms varying-sized aggregates, known as oligomers. Ever since the inception of the amyloid hypothesis, also referred to as the "null hypothesis", over a quarter of a century ago,

A β has been widely regarded as the principal etiological factor in Alzheimer's disease (AD) [21]. An alternative hypothesis posits that A β is a prodromal manifestation or simply the consequence of the disease rather than a causal factor for its development and progression. However, both models agree that the A β peptide is associated with the production of reactive oxygen species (ROS). The presence of several oxidative stress indicators in Alzheimer's patients' brains confirms that AD is characterized by ROS-induced oxidative stress [22]. The oxidative stress and damage is associated with a bioenergetic decline that in turn facilitates accumulation of toxic Ab.

The pathogenesis of Alzheimer's disease (AD) is also associated with detrimental changes in the cholinergic system, characterized by the employment of the enzyme acetylcholinesterase (AChE) to convert the neurotransmitter acetylcholine into choline and the acetate anion [23]. AChE has a CAS, or catalytic site, and a PAS, or peripheral anionic binding site. Acetylcholine is thought to first bind to the PAS before quickly diffusing to the CAS. Extensive cholinesterase enzyme, butyrylcholinesterase (BuChE), exhibits increased activity as the AD state worsens while AChE activity declines. The accumulation of the Abeta peptide is related to increased BuChE activity. Cholinesterase inhibitors (ChEIs) are used to increase cholinergic neurotransmission, which is the basis of the current medication for AD patients [24]. Amyloid plaques exhibited elevated levels of Cu, Fe, and Zn when subjected to certain physical techniques, namely scanning transmission ion microscopy, Rutherford backscattering spectrometry, and particle-induced X-ray emission, with meticulous attention to detail [25]. As a result, it was discovered that the amounts of copper, zinc, and iron were approximately triple that in the surrounding tissues. An accurate evaluation of redox-active transition metals, namely iron (Fe) and copper (Cu), together with the redox-inactive metal zinc (Zn), has identified a crucial new element linked to Alzheimer's disease (AD): The occurrence of oxidative stress induced by metallic elements [26,27]. Acetylcholinesterase (AChE) inhibitors, including donepezil (administered at dosages ranging from 5 to 10 mg per day), rivastigmine (often prescribed at dosages ranging from 1.5 to 6 mg per day), and galantamine (suggested at dosages ranging from 16 to 24 mg per day), have been authorized as pharmacological interventions for the clinical management of Alzheimer's disease [24]. Furthermore, memantine, an infrequently employed noncompetitive antagonist of the N-methyl-d-aspartate receptor, is suggested for administration at a dosage range of 5–20 mg/day [28]. These medications, while offering some relief, come with several unwanted side effects, including diarrhea, nausea, bradycardia, and potential liver toxicity. Furthermore, their primary limitation lies in their ability to only provide temporary symptom improvement without halting or altering the course of the disease. Despite amyloid β accumulation be-

ing a prominent hallmark of Alzheimer's disease, phase III trials involving anti-amyloid monoclonal antibodies such as bapineuzumab and solanezumab failed to demonstrate any significant enhancement in cognitive abilities among Alzheimer's patients [29].

The pivotal event triggering the onset of Alzheimer's disease is the enzymatic generation of the neurotoxic A β from APP [30]. To prevent A β synthesis, researchers developed and tested secretase inhibitors like semagacestat and avagacestat, targeting both β -secretase and γ -secretase, which play significant roles in this process [31]. However, the outcomes were not entirely conclusive, and adverse side effects emerged during these studies. Tau is a multifunctional protein crucial for stabilizing microtubules, and its significance in Alzheimer's disease (AD) has led to extensive research into both the protein itself and its phosphorylation. However, these investigations have yielded mixed results [32]. Certain research has associated the 'positive symptoms' of schizophrenia with the malfunctioning of the dopaminergic system within the mesolimbic pathway. In all phases of Alzheimer's disease (AD), there might be different degrees of dopamine insufficiency [33]. Additional investigation and rigorous clinical studies are necessary to enhance our understanding of the potential benefits of dopaminergic therapy in individuals diagnosed with AD [34]. Furthermore, it is essential to highlight the significance of dopaminergic dysfunction in the cognitive decline observed in persons with Alzheimer's disease. The intricate underlying processes of AD need a meticulously chosen mix of drugs that may impede the first pathological alterations and perhaps influence the progression of the condition [35]. As stated before, imbalances in metal homeostasis result in metal-induced oxidative stress, a phenomenon identified in the cerebral tissue of individuals diagnosed with Alzheimer's disease (AD). Oxidative stress represents a pivotal pathophysiological factor in several age-related ailments, including AD, cardiovascular diseases, cancer, and various neurological disorders. The efficacy of supplements in lowering oxidative stress remains uncertain due to the absence of agreement and definitive data. Nevertheless, it seems that the inherent antioxidants present in fruits and vegetables, especially when paired with various other antioxidants, might potentially alleviate the adverse effects of oxidative stress, particularly during the first phases of disease development and advancement [36]. AD impacts a significant number of individuals globally, although now, only symptomatic relief therapies are available. According to current projections, it is anticipated that around 5.8 million individuals in the United States who are 65 years old or older would be affected by AD in the year 2020 [37]. According to the predominant theory, tau and Ab proteins impair the energy supply and antioxidant defenses of neuronal cells in AD, resulting in dysfunction in both mitochondria and synapses. Neurons, due to their high energy requirements, are particularly susceptible to disrup-

tions in mitochondrial function associated with reduced antioxidant protection and bioenergetic decline. Regulating the levels of second messengers like calcium ions (Ca²⁺) and reactive oxygen species (ROS) is among the numerous processes crucial for the survival and demise of the cell. Moreover, mitochondria are involved in the production of intracellular energy in the form of adenosine triphosphate (ATP) [38,39]. Importantly, when mitochondrial function is impaired, it has a substantial effect on the synthesis of ATP, disturbances in calcium ion (Ca²⁺) equilibrium, and the formation of ROS. In the early stages of AD, alterations in mitophagy and mitochondrial dynamics are observed, but the underlying processes remain inadequately understood [40]. To enhance our comprehension of the development of this neurodegenerative condition and potentially advance therapeutic strategies aimed at preserving synaptic activity and, consequently, cognitive function, research must be conducted to elucidate the mechanisms underlying mitochondrial abnormalities in AD [41]. Recent research has demonstrated that indicators of oxidative stress can be detected at the initial phases of Alzheimer's disease (AD) [42]. Similarly, an impaired bioenergetic state resulting from mitochondrial inadequacy has been associated with pre-symptomatic AD. Apart from reduced ATP production, mitochondrial insufficiency leads to an excess of ROS which has been associated with cell death, changes in the cytoskeleton and degradation of cellular membranes. The exact correlation between oxidative stress and other indicators of the degenerative progression of Alzheimer's disease remains uncertain, despite the multitude of biochemical hypotheses that have been offered to explain their complex interaction and development [43]. Frailty's development is influenced by various factors such as oxidative stress, inflammation, dietary habits, obesity, blood clotting, and insulin resistance, as indicated by numerous studies [2,5]. Many of these studies involve older individuals living in communities who do not have AD but are part of population-based research with either no cognitive impairment or mild cognitive impairment [44]. Several biological components have been associated with degenerative processes in AD, such as β -amyloid and tau pathology. Interestingly, we have observed that while some AD patients experience frailty, others do not. It is worth noting that no research has delved into the biological mechanisms underlying frailty in AD patients so far. A rare case involving a 51-year-old patient who presented with symptoms including memory loss, disorientation, hallucinations, and cognitive decline was documented by Alois Alzheimer in his essay "Über eine eigenartige Erkrankung der Hirnrinde" ("On an Unusual Illness of the Cerebral Cortex") [45]. Upon the patient's demise, post-mortem examination revealed an atrophic brain displaying conspicuous alterations in neurofibrils and tiny localized areas of damage caused by the accumulation of a distinct substance within the cortex. This event signified the commencement of what is presently rec-

ognized as AD, a disorder that continues to be the most widespread neurodegenerative ailment after a century of scholarly investigation [46].

On a global scale, the World Alzheimer Report from 2015 reported that 46.8 million individuals were living with dementia, and this number is projected to nearly quadruple every 20 years [47]. Dementia affects approximately 5–8% of people over the age of 65, 15% of individuals over 75, and 25–50% of those over 85. In terms of regional distribution, Asia has the highest incidence with 22.9 million cases, followed by Europe with 10.5 million, and the Americas with 9.4 million [48]. It is worth noting that AD constitutes a substantial proportion of dementia cases, ranging from 50 to 75 percent. AD sufferers see a gradual deterioration in cognitive ability in comparison to persons who do not have the disorder. This decline is closely linked to a significant reduction in brain volume observed in AD patients. More specifically, the hippocampus experiences atrophy due to the loss of neurons and the deterioration of synapses [49], this brain region is responsible for spatial orientation and memory. The risk of developing AD rises up to 50% in individuals aged over 85, highlighting age as the most significant risk factor. Women have a higher likelihood of developing AD than men, possibly due to their longer life expectancy and the potential impact of reduced estrogen levels during menopause, which may increase the risk of AD. Extensive research is currently focused on a neurological disorder known as AD [50]. This condition has gained notoriety due to its increasing prevalence, particularly among older individuals, with the likelihood of developing it rising significantly with age. In fact, the incidence of Alzheimer's disease may approach 50% for individuals older than 90 years, and a European study revealed a 7.2% incidence rate among the population aged over 65 [51]. Initial indications of Alzheimer's disease often include deficits in short-term memory, difficulties in visuospatial perception and impairments in language and executive function. The disease can be diagnosed by observing a decline in cognitive abilities. One cost-effective diagnostic tool for this purpose is the Mini-Mental Status Exam (MMSE) test, which is considered a preferred choice in many healthcare systems over expensive laboratory tests relying on biochemical markers. Despite its simplicity, the MMSE test proves to be a robust tool for detecting the disease in its initial stages [52].

2.2 Factors Contributing in the Progression of Alzheimer's Disease

Oxidative stress is a condition characterized by the accumulation of reactive oxygen or nitrogen species to a level where the body can no longer effectively neutralize them. The connection between Alzheimer's disease and oxidative stress is under extensive investigation, and it appears to hold promise as a potential target for therapeutic intervention [53]. The relationship between Alzheimer's disease and oxidative stress has undergone thorough investigation

and appears to hold significant potential as a therapeutic target. This work examines the existing body of knowledge regarding oxidative stress in AD and the broad implications of using medicine to target the molecular mechanisms and mediators of the pathways implicated in oxidative stress and damage [54].

There is a great amount of research suggesting that oxidative and nitrosative stress significantly contribute to the progression of AD, resulting in the impairment of vital cellular elements like nucleic acids, lipids and proteins [55]. Oxidative stress (OS) occurs when the generation of reactive oxygen species (ROS) exceeds the cellular antioxidant defense system capacity. Likewise, OS arises as a result of the buildup of oxidized or impaired macromolecules that are insufficiently eliminated and replenished. The assemblage of antioxidant enzymes, comprising superoxide dismutase (SOD), glutathione peroxidase (GPx), glutaredoxins, thioredoxins and catalase (CAT), in conjunction with non-enzymatic antioxidant compounds, forms a fundamental defensive mechanism within the cellular environment [56]. Within the framework of AD, there is a decline or deterioration in the operation of antioxidant enzymes, as evidenced by a decrease in their particular activity. Indeed, several investigations have verified that dysfunction in mitochondria, principally caused by the production of ROS, plays a substantial role in the pathogenesis of AD [57]. The presence of A β peptides, in conjunction with trace metal ions like iron and copper, as well as altered mitochondrial function, have been identified as probable causes of OS. The incorporation of A β peptides into the cellular membrane has the potential to initiate the production of ROS, resulting in the peroxidation of lipids inside the membrane [58]. This process can subsequently cause harm to intracellular proteins and nucleic acids. Proteins have a heightened vulnerability to oxidative damage, which can induce significant modifications to their secondary and tertiary conformations, so causing enduring abnormalities in their structure and, subsequently, their functionality. The modifications may encompass processes such as the dissociation of subunits, unfolding of molecular structures, exposure of hydrophobic residues, aggregation of molecules, and fragmentation of the protein backbone.

Apart from these commonly observed protein modification markers, protein oxidation and nitrosylation can lead to S-nitrosylation and methionine oxidation (sulfoxidation). S-nitrosylation is a chemical reaction involving the cysteine group and N₂O₃, resulting in the formation of S-nitrosothiol (SNO). The control of SNO levels is quite complex, including the actions of nitrosylases and denitrosylases, which add or eliminate the NO modification, but also a homeostatic system of nitrosylated proteins. SNO modification plays a critical role in intracellular signaling based on redox reactions, and alterations in the SNO profile have been observed in Alzheimer's disease [59]. Over the course of more than thirty years of research, the Food and Drug Ad-

ministration (FDA) has granted approval for only five prescription drugs for Alzheimer's disease, and none of these medications target amyloid or tau. While these treatments do not provide a cure or a halt to the disease's progression, they are employed to address dementia-related symptoms such as memory loss and confusion. Galantamine, rivastigmine, and donepezil are administered to mild to moderate Alzheimer's patients, while memantine and memantine/donepezil are given to moderate to severe patients [60].

Regrettably, more than 200 phase II/III clinical trials assessing over 100 potential medications have experienced significant failures, resulting in substantial financial costs and decades of research efforts. Several methodological factors pertaining to the design of clinical trials for Alzheimer's disease (AD) have been related to these disappointments, including issues like inadequate dosing, insufficient bioavailability, challenges in patient recruitment/selection and compliance, inconsistencies in cognitive assessment methods, inappropriate timing of interventions, and difficulties in evaluating target engagement [61]. These issues raise questions about whether the current drugs are appropriately targeting the underlying pathological elements or if a multi-target approach is needed to bring about actual changes in the disease rather than just symptom alleviation. Several therapeutic strategies for Alzheimer's disease are currently in their preliminary or theoretical phases, undergoing experimentation in controlled laboratory settings or animal subjects, while others are now undergoing evaluation in clinical trials [62].

Currently, AD affects approximately 24 million individuals worldwide [63]. Magnetic resonance imaging (MRI) results often provide support for the clinical assessment of probable AD. However, a more precise pre-mortem diagnosis can be achieved through a positron emission tomography (PET) scan that examines amyloid β deposition or diminished 18F-fluoro-2-deoxyglucose uptake. Additionally, cerebrospinal fluid (CSF) analysis, which assesses amyloid beta peptide 1-42 ($A\beta$ 42), tau, and phosphorylated tau, can provide valuable diagnostic information. Post-mortem examination of brain histology demonstrates significant neuronal and synaptic deterioration, along with the existence of various amyloid plaques outside cells and the formation of neurofibrillary tangles inside neurons. These pathological features serve as confirmatory evidence for the analysis of Alzheimer's disease [64]. Increasing evidence indicates a link between AD and several variables, including mitochondrial failure, oxidative stress, and disruptions in autophagy [40]. Mitochondria are crucial for the proper functioning of neurons and any oxidative harm occurring within these mitochondria can have significant implications for the development of AD. Oxidative stress is acknowledged as a primary factor in cellular demise in neurodegenerative disorders, arising from an inequilibrium between oxidizing agents and systems that counteract their effects. Various research studies have demonstrated that au-

tophagy is suppressed in numerous neurodegenerative disorders, such as AD and Huntington's disease (HD) [40,65].

3. Role of Antioxidant Defense System in the Modulation of Alzheimer's Disease (AD)

Oxidative stress occurs when the creation of reactive oxygen species (ROS) exceeds the cell's ability to neutralize them via its antioxidant defense systems. The major defense against oxidative stress within the cell consists of antioxidant enzymes, including SOD, GPx, glutaredoxins, thioredoxins and CAT [66]. Furthermore, the defense mechanism is augmented by non-enzymatic antioxidant substances, including vitamin E, vitamin C, vitamin A, uric acid, and carotenoids. The brain is highly vulnerable to oxidative imbalances due to several contributing variables. The entity in question exhibits a notable requirement for energy, consumes a considerable quantity of oxygen, contains a profusion of readily peroxidizable polyunsaturated fatty acids, possesses a substantial amount of iron that assists as a potent catalyst for ROS, and has a comparatively restricted availability of antioxidant enzymes. Due to this confluence of elements, the brain is exceptionally susceptible to oxidative stress. Damage to numerous brain components, including membranes such as plasma and mitochondrial membranes and structural and enzymatic proteins, can result from oxidative stress [67]. Oxidative events have the potential to cause long-lasting changes in the tertiary structure and execution of proteins, as well as damage to nucleic acids. Moreover, the existence of A oligomers in the brain might worsen the situation by infiltrating membrane bilayers, leading to the production of reactive oxygen species (ROS) and the deterioration of intracellular proteins and nucleic acids. One of the very reactive byproducts of lipid peroxidation is 4-hydroxy-2-trans-nonenal (HNE), which is primarily produced in the brain by the peroxidation of arachidonic acid. Arachidonic acid is a prevalent omega-6 polyunsaturated fatty acid (PUFA) present in neuronal membranes [68]. HNE has the ability to affect ATP synthase, which is the last part of the electron transport chain (ETC) that is responsible for producing ATP in mitochondria. Despite the existence of antioxidants that function to protect the cell from the detrimental effects, a tiny quantity of superoxide anion ($\cdot O_2^-$) is consistently generated as a result of electron leakage, despite the great efficiency of the Electron Transport Chain (ETC) in energy generation [69]. Indeed, O_2^- can undergo a transformation into a non-radical compound, such as hydrogen peroxide (H_2O_2), either spontaneously or with the assistance of manganese superoxide dismutase found in the mitochondrial matrix. Copper, similar to iron, engages in the Fenton reaction, which enhances the production of ROS. Additionally, the Haber-Weiss reaction, which involves the direct interaction of O_2 with H_2O_2 , can also yield hydroxyl radicals ($\cdot OH$) [70]. Consequently, mitochondria are susceptible to oxidative harm, particularly oxidation mediated by

hydroxyl radicals, which is particularly relevant in the context of DNA oxidation. Mitochondria feature a robust antioxidant system comprising enzymes such as glutathione peroxidase, catalase, and peroxiredoxin III, which serves as a defense mechanism against the overproduction of ROS [71]. These enzymes have a vital function in facilitating the movement of electrons from nicotinamide adenine dinucleotide phosphate hydrogen (NADPH) to molecular oxygen, leading to the creation of water as the ultimate outcome. Due to its near proximity to the electron transport chain (ETC) and lack of histone protection, mitochondrial DNA (mtDNA) is especially vulnerable to oxidative damage. Oxidative damage vulnerability is evident in each of the four DNA bases, specifically thymine, adenine, guanine, and cytosine. In the context of brain aging, it has been shown that there is a discernible rise in oxidative harm to mitochondrial DNA (mtDNA). This is supported by the existence of OH8dG, which acts as the primary marker of DNA damage caused by oxidative stress [72]. The combination of heightened mtDNA oxidation and a deficiency in DNA repair mechanisms can potentially compound damage to the mitochondrial genome, potentially leading to neuronal harm. Based on the aforementioned assumption, it may be deduced that oxidative stress is commonly detected in AD, hence suggesting a substantial involvement in the genesis of the illness [73]. There exists a correlation between progressive mitochondrial malfunction and the processes of aging and Alzheimer's disease. The correlation may be ascribed to the role of mitochondria as the primary producers of ROS and their susceptibility to oxidative damage. The reciprocal relationship between oxidative stress and mitochondrial dysfunction is believed to contribute to the pathological progression of AD, hence exacerbating the detected abnormalities [41]. AD is hypothesized to arise from increased oxidative stress within the brain, which is stimulated by buildups of mercury, iron and aluminum. These deposits stimulate the generation of free radicals through the Fenton and Haber-Weiss pathways, resulting in escalated lipid peroxidation, oxidation of proteins and DNA, reduced energy metabolism, and the production of malondialdehyde [74]. Based on the existing body of evidence, it can be concluded that free radicals potentially play a role in the pathogenesis of cell death associated with AD. Conversely, antioxidant systems may significantly influence strategies for preventing and managing the condition [75]. The brain's capacity to mitigate the impact of oxidative stress is of utmost importance. A biological mechanism known as the thioredoxin system (TS) safeguards cells against oxidative injury. Thioredoxin (Trx), thioredoxinreductase (TrxR), and NADPH make up this system. The influence of TS proteins on antioxidant activities is of considerable importance. These proteins possess the capacity to influence the functioning and manifestation of other proteins, encompassing several transcription factors that are pivotal in cellular growth, as well as cell viability or pro-

grammed cell death [76]. Redox impairment occurs when there is an imbalance between the generation of free radicals from oxygen species and their conversion into intracellular inactive molecules. The production and aggregation of A β , as well as the hyperphosphorylation of tau protein, are aided by ROS. Additionally, the relationship between ROS and these processes is bidirectional [77].

While nuclear factors-activated- κ B (NF- κ B) was initially identified as a regulator of immunoglobulin production, it has since been established that this factor is ubiquitously present in all cell types. It has a regulatory function in the transcription of many genes, and this control happens in different physiological and pathological situations. Pro-apoptotic and pro-survival pathways, proinflammatory cytokines, antioxidant enzymes, pro-oxidant enzymes, and numerous others are encoded for these genes [78,79]. The presence of p65, which is a subunit of NF- κ B, has been notably detected in post-mortem brains of individuals with AD, and additionally, it is observed in both animal and cell-based models of AD. P65 is detected within amyloid plaques, neurons, and astroglia that encompass these plaques. This discovery is significant because it suggests that NF- κ B is triggered in Alzheimer's disease. Therefore, treatments that focus on NF- κ B have been proposed as a possible therapy strategy for AD [80].

To put it differently, oxidative stress is responsible for at least some of the toxicity associated with A β (Amyloid beta). A β has the ability to produce hydrogen peroxide (H₂O₂) by reducing metal ions. It may also increase the formation of free radicals when interacting with metals such as iron, copper, and zinc. These metals are found in high concentrations both in the centre and outer edges of A β deposits. The proteins undergo oxidative damage, leading to an elevation in carbonyl groups. Peroxynitrites are hypothesised to have a role in the brain, due to the formation of carbonyl residues and protein nitration, of persons bearing AD [81], indicating that they are exposed to high levels of reactive hydroxyl, carbonate and nitrogen dioxide radicals. Protein carbonyls, derived from amino acid residues including arginine, histidine, lysine, proline, threonine, and cysteine, are widely used biomarkers to evaluate protein oxidation and oxidative stress in the context of ageing and different illnesses [82]. Oxidative stress contributes to the advancement of brain ageing and the development of Alzheimer's disease. Both these processes are characterised by the presence of malfunctioning mitochondria, which produce free radicals as a byproduct of respiration. As per the mitochondrial cascade hypothesis, dysfunctional mitochondria have a role in generating amyloid beta, which in turn acts as a detrimental oxidative stress inducer [83]. Research has shown that administering mitochondrial antioxidants to older mice may significantly reduce oxidative stress and DNA damage. Additionally, the restoration of mitophagy in models of Alzheimer's disease can lead to a reduction in pathology. Free radicals are the causative

agents of DNA damage, with a significant portion of this damage occurring in mitochondrial DNA, which lacks histone protection. Alzheimer's disease is characterised by a significant rise in double-strand DNA breaks as compared to the ageing brain. Additionally, the presence of defective DNA repair pathways worsens the course of the illness [84]. Oxidative stress can impact the epigenome, resulting in many outcomes, such as the control of cognitive genes through H3K9me3-mediated pathways and the reduction of methylation and activation of the *APP* promoter. Oxidative stress, although not the main factor responsible for cognitive decline or neurodegeneration, does seem to play a role in the malfunctioning pathways linked to the ageing of the brain [85]. The efficacy of emerging treatments for oxidative stress in improving cognition and reducing ROS levels varies. Antioxidant treatments have demonstrated varied impacts on cognitive function in both older adults and patients with Alzheimer's disease. To achieve consistent outcomes, factors such as dosage, timing, combinations of antioxidants, and dietary considerations must all be carefully investigated [86].

3.1 Metabolic Stressors and Their Contribution in Alzheimer's Disease

ROS and RNS are generated as a result of regular metabolic processes or in response to cellular stressors, and they gradually build up in the body [87]. Extended exposure to ROS, in addition to its cumulative effect, results in cellular harm and hindered regeneration, which are strongly linked to age-related degenerative illnesses. The aged population is more vulnerable to degenerative illnesses due to elevated levels of pro-oxidant damage and a decline in antioxidant defence systems [88]. Neurons are highly active cells with a substantial oxygen demand, accounting for approximately a quarter of the body's total oxygen consumption [89]. Consequently, neuronal cells generate significant amounts of reactive oxygen species (ROS) and reactive nitrogen species (RNS), rendering them susceptible to free radical attacks. Neurons have relatively lower quantities of antioxidant defence molecules, such as glutathione (GSH), and a larger quantity of readily oxidizable polyunsaturated fatty acids, as compared to other types of cells. The existence of antioxidant enzymes, specifically hemeoxygenase (HO)-1 and superoxide dismutase (SOD)-1, within senile plaques provides significant evidence for the role of oxidative stress in the aetiology of Alzheimer's disease [90]. Notably, it has been shown that oxidative stress is an early occurrence in the progression of Alzheimer's disease. Elevated production and accumulation of ROS lead to increased levels of oxidized proteins, lipids, and DNA, which have been associated with Alzheimer's disease [67]. ROS molecules have been demonstrated to augment the synthesis, aberrant folding, and accumulation (crosslinking) of amyloid beta. Amyloid beta peptides typically consist of 40–42 amino acid

chains with the sequence: DAEFRHDSGYEVHHQKLVF-FAEDVGSNKGAIIGLMVGGVVIA. The peptides mentioned are generated by proteolysis of the amyloid precursor protein (APP) as a consequence of cleavage by beta and gamma proteases, frequently as a result of hereditary abnormalities in the *APP* gene. Methionine, which is located at position 35 in the Amyloid beta protein sequence, is an amino acid residue highly susceptible to oxidation. ROS can oxidize methionine side chains under physiological conditions, leading to the presence of oxidized forms of methionine in Alzheimer's disease brain tissue [91]. Methionine can be oxidized either by the addition of two electrons to form methionine sulfoxide or by the loss of one electron, resulting in a sulfuranyl free radical. The oxidative changes have the potential to induce harm to neighbouring neuronal proteins and lipids [92].

AD is linked with the occurrence of lipid oxidation in the brain tissue, which is a degenerative characteristic [93]. The brain contains highly susceptible polyunsaturated fatty acids, including arachidonic and docosahexaenoic acids, which are prone to oxidation. Lipid peroxidation causes the degradation of neuronal membranes and produces several secondary substances including 4-hydroxy-2-nonenal, acrolein, isoprostanes, and neuroprostanes. A specific investigation found elevated levels of the lipid peroxidation biomarker called thiobarbituric acid reactive substances (TBARS) in the synaptosomal membrane portion of neurons impacted by Alzheimer's disease [94]. Alzheimer's disease is linked to oxidative damage of DNA, along with the oxidation of amyloid beta and lipid peroxidation. Reactive oxygen species (ROS) can damage DNA by causing uncontrolled alterations to nucleic acid bases [95]. Hydroxyl radicals have the ability to alter guanine nucleotides, resulting in the creation of 8-hydroxy guanine. This altered guanine has a propensity to form base pairs with adenine rather than cytosine. The oxidation of thiamine may lead to the creation of hydrogen bonds between 5-hydroxymethyluracil and adenine, enabling their coupling. In addition, reactive nitrogen species (RNS) and peroxynitrous acid have the ability to interact with nucleic acid bases, resulting in oxidative deamination by substituting NH_2 groups with OH groups. The uncontrolled process can convert adenine, cytosine, and guanine into hypoxanthine, uracil, and xanthine, respectively. Hypoxanthine and uracil can both create erroneous base pairs with cytosine and adenine. The occurrence of oxidised DNA bases in the brains of individuals with AD, such as 8-hydroxyadenine, 8-hydroxyguanine, thymine glycol, Fapy-guanine, 5-hydroxyluracil, and Fapy-adenine, strongly emphasises the important contribution of DNA damage to the development of AD [96]. Researchers have discovered a much greater quantity of damaged DNA in neurons that have been exposed to A β peptides in individuals with AD [97]. Various metal ions, such as copper, iron, aluminium, lead, mercury, manganese, and zinc, are essential for main-

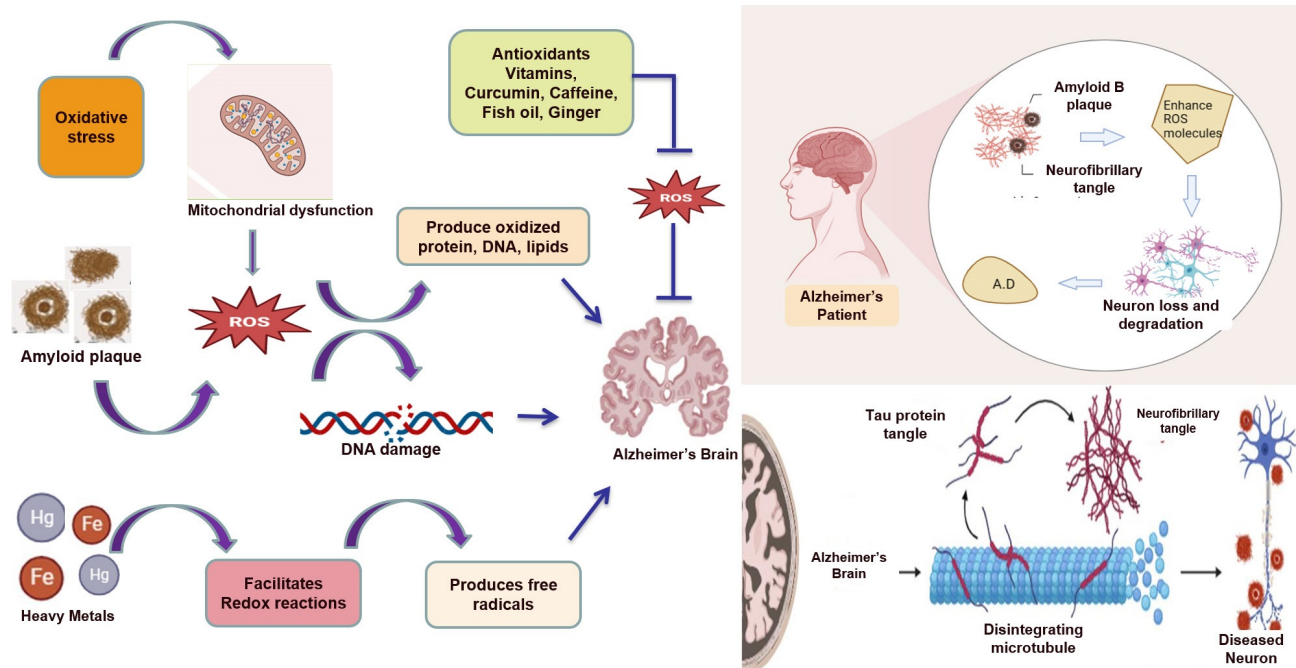


Fig. 1. Amyloid beta plaques, neurofibrillary tangles, and heavy metals all contribute to the production of reactive oxygen species (ROS) and, ultimately, Alzheimer's disease. Antioxidants can inhibit the formation of ROS and protect against neurodegeneration in Alzheimer's disease.

taining cellular homeostasis. Nevertheless, heightened concentrations of toxic metals have been identified in the cerebral tissue of patients afflicted with Alzheimer's disease. Multiple studies have confirmed that interactions between metal ions and APP and amyloid beta peptides lead to an increase in the generation of ROS, which, in turn, results in the overproduction and accumulation of amyloid beta peptides and heightened neurotoxicity [54,58,62,98]. Heavy metal ions behave as potent pro-oxidants and facilitate redox processes that generate free radicals that are highly reactive, such as hydroxyl radicals. Lead and mercury, in particular, have been associated with increased expression of APP, heightened reactivity of glial cells, neuronal inflammation, and oxidative stress [99].

3.2 Various Biomolecules as Prognostic Indicators of Alzheimer's Disease

ROS are endogenously generated as a result of normal metabolic processes within cells in living organisms [100]. ROS play a crucial role in preserving cellular balance and are implicated in several physiological processes, such as immunological responses and inflammation. The overproduction of ROS may be harmful, leading to oxidative harm to cell components, particularly the delicate mitochondrial structures that are highly susceptible to ROS-induced injury [101]. Given its substantial oxygen demand for proper functioning, the brain is particularly susceptible to the deleterious effects of ROS. In addition, the brain contains a limited number of enzymes and other antioxidant molecules,

a substantial amount of iron (a potent catalyst for reactive oxygen species), and peroxidation-sensitive polyunsaturated fatty acids. Therefore, oxidative stress plays a substantial role in the advancement of neurodegenerative diseases, including AD. The biomolecules that experience the highest levels of oxidation in AD are the ones present in neuronal membranes, such as lipids, fatty acids and proteins. Changes in biomarker levels can function as prognostic indicators of AD, where oxidative stress is a pivotal contributor to its development and progression [102]. ROS are amphiphilic compounds distinguished by their unpaired electron that gives them their exceptionally high reactivity and short lifetime. Upon oxidation of biomolecules, the resultant species exhibit enhanced stability compared to the initial molecules and can serve as indicators of oxidative damage. Nucleic acids, proteins, and oxidised lipids are a few examples of these biomarkers. Biomarkers may also consist of variations in the concentrations of antioxidant enzymes such as glutathione peroxidase, superoxide dismutase, and catalase, in addition to other antioxidant compounds. Due to their properties, antioxidant molecules hold promise in preventing and treating disorders related to oxidative stress, including neurodegenerative diseases [103]. Antioxidants consist primarily of compounds that possess the capacity to scavenge free radicals, thereby preventing the chain reaction of the radical propagation and reinstating the stability of the molecules involved.

Iron is a vital constituent of the human body, and its iron (II) forms, such as iron (II) ions or iron (II)L com-

plexes (where L is a coordinated ligand), can engage in chemical processes referred to as Fenton or Fenton-like reactions. These reactions involve the combination of iron with H_2O_2 to produce hydroxyl radicals ($\cdot OH$). The hydroxyl radical, possessing a substantial electrode potential has remarkable reactivity and may swiftly engage with diverse biomolecules via mechanisms such as hydrogen abstraction and hydroxyl addition which leads to oxidative adverse effects on DNA, proteins, and cells. Oxidative damage to biomolecules takes place inside a living organism when the body's antioxidant defences, such as enzymes and natural antioxidants, are unable to cope with the excessive creation of ROS, thereby disturbing the balance between prooxidation and antioxidation (Fig. 1). Multiple studies have presented compelling data establishing a significant connection between oxidative stress and neurodegenerative illnesses, namely AD and Parkinson's disease (PD), particularly in the specific areas of the brain that are afflicted [8,27,36,64,104]. Iron, being the transition metal most abundant in a healthy brain, is essential for optimal brain function. Copper and zinc, among other transition metals associated with AD pathology, are present in trace quantities. However, the initial phases of AD progression are distinguished by the existence of iron accumulation and oxidative stress.

Increased concentrations of redox-active iron have been suggested as possible catalysts for the clumping together of amyloid- β ($A\beta$) and the occurrence of oxidative harm in the brain [105]. Ferroptosis, an iron-dependent pattern of cell death that has recently been identified, is thought to be induced by the buildup of ROS composed of lipids. It is also considered to be a major cause of cell death in neurological disorders including AD and PD. Hence, in order to progress the pharmaceutical therapies for neurodegenerative disorders, it is imperative to acquire a more profound comprehension of the functions of iron and the resulting oxidising species [106]. Significantly occurring primarily within mitochondria, ROS are generated by mitochondrial enzymes. Single-electron leakage is a process by which the electron transport chain (ETC) within mitochondria generates superoxide radicals; this occurs primarily during respiratory phases I and III of the oxidative phosphorylation (OXPHOS) pathway [107]. Nevertheless, it is crucial to acknowledge that the rate of reactive oxygen species (ROS) production in complex I is comparatively lower than that of Flavin-dependent enzymes present in the mitochondrial matrix. Under normal physiological circumstances, researchers have extensively examined five distinct antioxidant enzymes that are found within cells: (i) Cu/Zn-SOD or SOD1, which is located in the cytosol, (ii) Mn-SOD or SOD2, located in the matrix of the mitochondria, (iii) CAT, (iv) GPx and (v) additional secondary antioxidant and cellular detoxification systems.

The regulation of these secondary systems is predominantly carried out by Kelch-like erythroid-derived

cap'n'collar homolog (ECH)-associated protein 1 (Keap1) and NF-E2-related factor 2. Keap1 typically acts as an actin-binding protein that keeps Nrf2 in the cytoplasm. It functions as a protein that binds to a substrate and facilitates its interaction with the Cullin3-containing E3-ligase complex [108]. This intricate molecule specifically targets Nrf2 for the process of ubiquitination and subsequent destruction by the proteasome. Crucially, Keap1 is responsive to changes in redox state and can be altered by different oxidising agents and electrophiles. Oxidative stress (OS) hinders the breakdown of Nrf2 by Keap1, resulting in the buildup of Nrf2 in the nucleus [109]. Within the nucleus, Nrf2 combines with a small musculoaponeurotic fibrosarcoma (Maf) protein to create heterodimers, which then attach to antioxidant response elements (AREs). This relationship is responsible for the stimulation of the synthesis of phase II antioxidant enzymes, which include glutamate-cysteine ligase, glutathione S transferases (GSTs), NAD(P)H quinone oxidoreductase 1 (Nqo1) and heme oxygenase 1 (Hmox1). In addition, Nrf2 is involved in maintaining cellular proteostasis via controlling the expression of molecular chaperones and different subunits of the proteasome [110]. Aside from antioxidant enzymes, the cellular components are shielded from reactive oxygen species (ROS) by small molecules and non-enzymatic antioxidants, such as natural flavonoids, vitamins, thiol antioxidants and carotenoids. Antioxidants play a crucial role in protecting cellular components against oxidative injury [111]. While adequate level of ROS are critical for the proper functioning of physiological systems, elevated levels have been associated with oxidative damage to various cellular components and compartments. The oxidative damage manifests as structural and functional anomalies in macromolecules, specifically lipids and proteins, distributed throughout many brain areas. For instance, elevated levels of oxidative stress linked to cell membranes have been identified in brain tissue from individuals with AD. The elevated levels of oxidative stress detected are correlated with the buildup of cholesterol and ceramides in clustered microdomains within samples of brain tissue affected by AD [112]. Notably, antioxidants like vitamin E and ceramide inhibitors have been shown to prevent the formation of these microdomains. The formation of such microdomains has been extensively studied, with one significant finding being that the aggregation of extracellular A beta at the cell membrane leads to oxidative damage associated with the membrane. The oxidative stress occurring at the membrane level is distinguished by the process of lipid peroxidation, which leads to the formation of the neurotoxic compound known as 4-hydroxynonenal (HNE). Hydroxynonenal (HNE) has been identified in the first phases of AD advancement and exhibits a clear correlation with the extent of neuronal damage and degeneration [113]. Furthermore, it has been observed that oxidative stress has the ability to stimulate pathways that are associated with the pathogenesis of AD. An exam-

ple of this is the activation of the mitogen-activated protein kinase (MAPK) p38 in response to oxidative stress induced by A beta. One of the many roles of p38 is to stimulate the phosphorylation of tau in primary neuronal models. This process can be blocked by administering a p38 inhibitor or vitamin E before the therapy [114]. The veracity of these findings has been validated *in vivo* by the utilisation of an APP/PS1 transgenic mice model for AD. Oxidative stress associated with Alzheimer's disease leads to significant deterioration of nucleic acids through oxidation. This damage leads to alterations in the structure of DNA. Mitochondrial DNA and RNA have also been found to be oxidized in various diseases, not just Alzheimer's disease [113]. One specific aspect of DNA/RNA oxidation is the conversion of guanosine to 8-hydroxyguanosine (8-oxoG). Autopsy study of brain tissues from Alzheimer's disease patients have revealed high levels of 8-oxoG in neurons in regions such as the hippocampus, subiculum, entorhinal cortex, and various neocortical areas [115]. Furthermore, RNA oxidation in the frontoparietal cortex, hippocampus, cortical neurons, and white matter of aged rats has increased significantly. These findings indicate that the damage caused by oxidative stress to DNA and RNA adds to the progress of neurological disorders and the ageing process. Additionally, both amyloid beta (A β) and tau proteins exhibit various alterations in response to oxidative stress. Tau is involved in the organization of microtubules by dynamically interacting with newly formed microtubules [116]. In AD patients, intracellular dynamics related to microtubule structure have been found to be disrupted. Exposure to substances like hydrogen peroxide (H₂O₂) or 4-hydroxynonenal (HNE) has been shown to reduce microtubular network growth in numerous cell lines, including ventricular myocytes, neuro-2A cells, rat pheochromocytoma PC12, and the pancreatic epithelial cell line AR42J [113]. This reduction is primarily mediated by Michael addition reactions. On one end of the spectrum, there is full acceptance of the role of oxidative stress as the causative pathological process initiating diseases like Alzheimer's disease. On the other end, there is skepticism about the physiological relevance of oxidative stress. In between these extremes, there are balanced views and hypotheses. Some propose that oxidative stress is a co-factor that exacerbates the progression of Alzheimer's disease but doesn't necessarily initiate it. In its mildest form, oxidative stress is considered to constitute a sole marker without a causal impact. The presence of several viewpoints results in different understandings of oxidative stress in AD. Due to the ambiguous nature of the actual cause of AD, it is difficult to properly evaluate the impact of oxidative stress. With the production of significant quantities of ROS and utilisation of more than 20% of the total ambient oxygen supply, the brain is among the most metabolically active organs in the body. In healthy conditions, mitochondria produce ROS, including superoxide anion (O₂⁻), hydroxyl radical (OH), and hydrogen peroxide (H₂O₂), as

well as reactive nitrogen species (RNS) like nitric Oxide (NO) and peroxynitrite (ONOO) [117]. The negative effects of free radicals are mitigated by antioxidant enzymes, including as SOD, GPX, CAT and different chelating proteins that lie within the antioxidant system, which combat these reactive species. Presently, it is postulated that the occurrence of oxidative stress in individuals with AD might be initiated by one or more causative factors. The most widely recognized factors include the presence of amyloid plaques, elevated levels of heavy metals, and mitochondrial dysfunction [118]. A recent investigation has demonstrated that the dysregulation of redox state significantly worsens AD and activates numerous cellular pathways implicated in the pathogenesis and progression of this neurodegenerative condition [119]. Consequently, oxidative stress should now be considered a critical player in AD and many other forms of dementia. Several empirical observations now demonstrate a strong correlation between oxidative stress (OS) and cellular mechanisms that result in neuronal damage, such as the generation of beta-amyloid, formation of Neurofibrillary Tangles (NFTs), inflammation of the brain and aberrant mitochondrial activity. These elements collectively form a complex cycle of events in which OS plays a pivotal role. Therefore, simultaneously modulating OS and suppressing other characteristics of Alzheimer's disease (AD) could potentially lead to more promising treatment approaches compared to currently available options [120]. Recent evidence suggests that attempts to decrease the overall levels of reactive oxygen species (ROS) in the body may be futile because of the dual function of ROS. On one hand, increased ROS production contributes to the development of age-related chronic illnesses and neurodegeneration. Conversely, oxidants like superoxide and hydrogen peroxide can function as signaling molecules in numerous vital redox-dependent signaling pathways crucial for an organism's survival. These pathways encompass epidermal growth factor receptor signaling, inactivation of the tumor suppressor Phosphatase and tensin homolog (PTEN), regulation of circadian rhythms, modulation of the inflammatory response, and the hormetic stress response. Hence, maintaining redox balance with precise control over ROS production levels is essential to safeguard cells against oxidative stress while ensuring the availability of vital electrophilic signaling molecules that act as endogenous messengers that enable and orchestrate hormetic adaptation and synaptic plasticity. Understanding how ROS's dual role is maintained throughout the aging process and during different stages of disease is of paramount importance for the development of therapeutic strategies targeting ROS generation and detoxification [121]. The brain is particularly vulnerable to oxidative stress due to its high concentration of polyunsaturated fatty acids, limited antioxidant capacity, and elevated oxygen requirements [122]. Oxidative stress is associated with certain neurodegenerative conditions, such as Alzheimer's and Parkinson's disease. Oxidative stress is

caused by the disparity between ROS and RNS, which encompass radicals such as H_2O_2 , OH, O_2 , Nitrogen dioxide radical (NO_2), and others. Several studies have reported imbalances in trace elements such as Al, Si, Zn, Cu, and Fe in Alzheimer's disease. Oxidative stress is a pathological process associated with aging, including Alzheimer's disease. It has been observed that oxidative stress occurs early in AD and is a major contributor to the formation of NFTs in AD [26,54,62,123].

Nitric oxide synthase catalyses the conversion of arginine to citrulline, resulting in the synthesis of nitric oxide (NO). NO has the tendency to interact with O_2 , resulting in the formation of peroxynitrite (ONOO). In the presence of reduced transition metals ($Fe^{+2/+3}$), H_2O_2 is converted into the harmful hydroxyl radical (HO) through Fenton and/or Haber-Weiss reactions [124]. The HO radical has the potential to cause oxidative damage to lipids, proteins, DNA, and carbohydrates. Impairment of the electron transport chain (ETC) results in the failure of the antioxidant system to counteract reactive oxygen species (ROS), causing an elevation in ROS generation and subsequent neuronal damage. The coexistence of okadaic acid and oxidative stress in AD results in an upregulation of tau protein phosphorylation and neuronal demise. It is important to mention that ROS and RNS can exert either harmful or advantageous impacts on biological systems [125].

4. Antioxidants in Alzheimer's Disease

Antioxidants are like protective substances that help reduce the damage caused by oxidative stress. Oxidative stress is when harmful molecules in our body cause damage and induce degeneration. Antioxidants work in two ways: Primary antioxidants and secondary antioxidants. Primary ones fight against harmful molecules and stop them from causing damage, while secondary ones help other antioxidants work better. These antioxidants are important because they can help prevent health problems like Alzheimer's disease [73]. Our body has a natural defense system against these harmful molecules, and we can also get antioxidants from the food we eat. There are two types of antioxidant systems: one that our body makes on its own, and another that comes from the food we eat. Some important antioxidants in our body include glutathione peroxidase, catalase, and vitamin C. They help get rid of harmful molecules and keep our cells healthy [126]. The impact of nutrition on both cognitive and physical well-being is generally recognised. Multiple studies have demonstrated that dietary sources have a substantial impact in addressing AD [90,99,127]. Natural dietary antioxidants such as Vitamin C, E, carotenoids, flavonoids, polyphenols, and other compounds are part of this category. Furthermore, both literary sources and empirical research suggest that a suitable diet incorporating vitamins, proteins, and minerals can successfully supplement the medicine used in the treatment of AD. In addition, apple cider has been demonstrated to augment

the activity of SOD, CAT and GPx in order to diminish lipid peroxidation, according to stated sources [128].

Dietary potassium plays an important role in diminishing reactive oxygen species (ROS), modifying the pattern of $A\beta$ aggregation, and contributing to cognitive enhancement. Moreover, a proper increase in dietary potassium, within optimal levels, offers advantages by guarding against age-related and diet-related neurodegenerative disorders [128]. Garlic and its constituents exhibit a positive impact on brain function and neuronal processes, potentially serving as a treatment for AD. The presence of flavanone glycosides in citrus fruits may be associated with the modification of beta-amyloid precursor protein cleaving enzyme 1, hence impacting its structure. Fasting overnight with soaked almonds enhances memory in C57Bl/6 mice and Sprague-Dawley rats, perhaps attributed to the presence of vitamin E [128]. However, despite limited research, the comprehensive impact of dietary choices and eating patterns on Alzheimer's disease (AD) remains uncertain when examining cross-sectional studies [129]. Therefore, further investigation in this field is necessary. Moreover, individuals lack enough understanding regarding the precise amount and calibre of bioactive constituents included in food products, which hinders the attainment of significant neuroprotection. Vitamin E is involved in the removal of free radicals from the membranes of red blood cells and the prevention of the progression of lipoperoxidation. It is worth mentioning that α -tocopherol, which is the main kind of vitamin E, is easily absorbed by human tissues. It may assist to counterbalance the increased production of alpha-tocopherol transfer protein (α -TTP) in the brains of people with Alzheimer's disease [130]. Meta-analytical studies reveal reduced concentrations of vitamin E in the blood plasma of individuals with AD [128,130]. Several clinical investigations indicate that vitamin E and *Ginkgo biloba* extract show promise in enhancing cognitive brain function. There is strong data indicating that vitamin E is useful in reducing the harmful effects of tau on the nervous system in *Drosophila*. A new study suggests that vitamin E effectively decreases oxidative and nitrosative damage in Alzheimer's disease (AD) [126].

Resveratrol, a kind of caloric restriction mimetic, has been proven to decrease oxidative stress in neurons in both, in *in vivo* rodent and *in vitro* neuronal cell models. It has also been shown to alleviate cognitive loss in persons diagnosed with Mild Cognitive Impairment (MCI) and Alzheimer's disease (AD) [131]. Nevertheless, the potential therapeutic impacts of these mimetics on the process of brain ageing have not been sufficiently investigated. The majority of persons find it difficult to adhere to long-term caloric restriction, and the effects of this restriction on cognitive ageing have not been thoroughly investigated. Clinical trials investigating caloric restriction frequently encounter constraints regarding the length of time and the degree of caloric restriction. Moreover, investigations em-

ploying caloric restriction mimetics have shown inconclusive outcomes [132]. In contrast, long-term exercise appears to be a more feasible approach to stimulate brain-derived neurotrophic factor (BDNF) production and create lifelong hormetic conditions compared to caloric restriction [133]. Clinical research on the long-term effects of exercise is becoming more prevalent, which is an encouraging development. Nevertheless, there is a requirement for comprehensive and extensive exercise intervention studies that address both the typical deterioration in cognitive function associated with ageing and the progression of Alzheimer's disease. Several clinical studies often employ small and homogeneous sample sets to investigate the effects of exercise over very brief periods [133,134]. Therefore, it is essential for investigations to broaden the scope, diversity, and duration of their exercise interventions. This may involve comparing individuals who have exercised throughout their lifetimes with those who have been inactive in their older age. It is crucial for clinical studies to not only assess cognitive indicators but also to examine oxidative stress markers in order to gain a better understanding of their role in the cognitive benefits induced by exercise. Research has demonstrated that engaging in exercise over an extended period of time can decrease the detrimental consequences of oxidative stress, promote the return of antioxidant activity, decrease the presence of disease indicators, and improve the brain's ability to withstand toxic substances. Among the known treatments, long-term physical exercise holds the greatest potential for reducing oxidative stress while supporting the optimal balance of stressors required for optimal brain function [22].

Alzheimer's Disease and the Significance of Nutrients

In addition to their antioxidant properties, natural substances have shown other crucial attributes in countering the advancement of AD through anti-inflammatory responses, warding off A β aggregation, suppression of tau protein accumulation and enhancement of cholinergic signal transmission. NF- κ B inhibitors, including alkaloids like cryptolepine and tetrandrine, are therefore classified as anti-inflammatory pharmaceuticals [135]. Flavonoids, known for their capacity to inhibit inflammatory reactions, exhibit potential in countering the progression of AD. In research conducted with animal models of AD, compounds known as terpenoids, including artemisinin, parthenolide, and carnosol, have been investigated to block the NF- κ B and p38 MAPK pathways. Ginsenoside Rg1, extracted from the roots of the Ginseng plant, has demonstrated a notable capacity to effectively reduce A β peptide levels in mice afflicted with Alzheimer's disease (AD) [136]. Natural botanical substances, including crocin, α -cyperone, chrysophanol, and aloe-emodin, have demonstrated the ability to inhibit the development of tau proteins and slow down the development of AD [137].

Vitamin A

Vitamin A and its related compounds, known as retinoids, play important roles in various essential processes in the brain. These processes include the development of brain cells, the release of chemical messengers between nerve cells, and the strengthening of long-term memory [138]. Additionally, they have properties that protect against cell damage from harmful molecules called free radicals. Moreover, vitamin A and its derivatives can influence how genes work by interacting with specific receptors called retinoic acid receptors (RARs) and retinoid X receptors (RXRs), which act like switches for gene activity. AD patients have a significant reduction in blood levels of beta-carotene and vitamin A. Interestingly, higher levels of beta-carotene in the blood are linked to better cognitive abilities in older individuals. The production of retinoid acid, a type of vitamin A, is reduced in response to A β peptides, which are linked to AD [139]. This reduction occurs through a mechanism involving Retinoic acid receptor (RAR α) indicating that vitamin. Elevated concentrations of A β peptides inhibit their synthesis in tissues, including brain tissue affected by AD. Adult rats with Vitamin A deficiency exhibit increased accumulation of A β deposits in their brain tissue and cerebral blood vessels. A recent study revealed that mice with a vitamin A shortage had elevated A β formation in their brain tissue. Additionally, there was a drop in the quantity of soluble amyloid precursor protein alpha (sAPP α), indicating a change from a less detrimental processing of the protein termed APP to a more destructive one [12]. In a mouse model of AD with two genetic changes, treating them with all-trans retinoic acid for eight weeks resulted in a significant reduction in A β accumulation in the brain and improved cognitive function. Mice with chemically-induced dementia, specifically using streptozotocin, had comparable impacts on cognition and the presence of A β plaques when administered all-trans retinoic acid. Additionally, these animals exhibited reestablished functionality of the enzyme acetylcholinesterase, diminished detrimental alterations induced by oxidative stress, and decreased concentrations of the inflammatory marker myeloperoxidase [140]. Moreover, administration of a RAR α activator to APP/tau-double transgenic mice led to a drop in the quantity of A β plaques in their brains and enhanced cognitive function. The administration of the RAR α activator in mice resulted in the activation of enzymes such as neprilysin (NEP) and insulin-degrading enzyme (IDE) in microglia. This activation might potentially aid in the reduction of the accumulation of A β [141]. Moreover, vitamin A might also have an impact on another problem in Alzheimer's disease called tau pathology. When administered all-trans retinoic acid, a kind of vitamin A, mice with genetic alterations resembling Alzheimer's disease exhibited reduced quantities and smaller aggregates of tau protein in their brain tissue, as shown in several investigations. This impact may arise

due to a reduction in the activity of certain enzymes (Cdk5 and GSK3 β) implicated in tau-related matters [142]. Similar benefits in reducing tau phosphorylation, a process related to tau problems, were observed in mice with AD-like characteristics when they were treated with RAR α activators or retinoic acid [143]. However, it's important to note that there have been no experiments conducted on humans to investigate how vitamin A supplements might affect the progression of Alzheimer's disease. The influence of vitamin A and its associated chemicals on A β levels in the brain can be partly elucidated by their regulation of genes associated with Alzheimer's disease. These genes include those responsible for making proteins like APP, beta-site APP-cleaving enzyme 1 (BACE1), ADAM, 9PS1, PS2, IDE and ADAM 10 [144]. Additionally, vitamin A appears to influence the processing of APP by changing how certain proteins are moved within cells. More precisely, studies have demonstrated that all-trans retinoic acid facilitates the translocation of proteins like as ADAM9, ADAM10, and BACE1 to the cellular membrane. This translocation mechanism leads to a more favourable processing of APP, preventing the detrimental accumulation of A β [145,146]. Moreover, laboratory investigations have revealed that vitamin A and beta-carotene can interfere with the aggregation of A β proteins and destabilise pre-existing A β complexes. This disruption is most likely caused by the binding of the compound to the terminal portion of the A β peptide [147].

Vitamin E

Vitamin E, a lipid-soluble antioxidant, has a crucial function in protecting the human body from oxidative harm. Vitamin E is available in eight distinct natural forms, which are categorised into four tocopherols and four tocotrienols. These forms are represented by the Greek letters α , β , γ , and δ . Beyond their antioxidant function, these compounds also influence gene expression and signal transmission, and they can regulate inflammation and cellular processes by interacting with specific parts of cell membranes [148]. Telomeres, which are repeating sequences found at the ends of chromosomes, serve to protect them from degradation and fusion. Over time and with cell divisions, telomeres shorten, which can lead to DNA damage, cell senescence, or cell death. The length of leukocyte telomeres (LTL) appears to decrease with age, potentially serving as a marker of biological aging. In neurodegeneration, LTL has been linked to cognitive decline in older adults and those with AD. However, the connection between LTL and AD's development is still debated, as some studies have found shorter telomeres in AD patients, while others have not found significant differences compared to healthy individuals [149,150]. There is a lack of consensus on the correlation between various types of vitamin E and LTL, as well as the association between these types and the underlying processes of AD. However, vitamin E may have the ability to safeguard telomeres and decelerate cellu-

lar ageing, owing to its antioxidant and anti-inflammatory characteristics. The decreases in α -, γ -tocopherol, and δ -tocotrienol were particularly remarkable, with percentages that were 20.4%, 14.0%, and 61.5% lower than the control treatments (CTs), respectively. Moreover, oxidative/nitrosative damage indicators revealed higher values in AD patients for α -tocopherylquinone/ α -tocopherol and 5-nitro- γ -tocopherol/ γ -tocopherol. This data supports the idea that low vitamin E concentrations could pose a risk factor for AD in older individuals. Notably, α - and β -tocopherol, δ -tocotrienol, total tocopherols, total tocotrienols, and total vitamin E seem to be particularly involved in the risk assessment for AD. Recent research indicates that α -, γ -, and δ -tocopherol have antioxidant and anti-inflammatory properties that could contribute positively to the development of chronic diseases [151]. For example, mixed tocopherol supplementation might be more effective than supplementing with α -tocopherol alone. Additionally, δ -tocotrienol has been shown to modulate inflammation, especially regarding TNF- α concentrations [152]. Vitamin E is a powerful antioxidant that is especially effective against harmful molecules called peroxy radicals. It can work on fats found in cell membranes and low-density lipoproteins in the body. It has the potential to slow down or prevent nerve cells from dying due to inflammation. Additionally, it can get rid of harmful molecules called free radicals in the outer covering of red blood cells and prevent damage caused by certain fats. Alpha-tocopherol is the predominant and beneficial form of vitamin E, readily absorbed by the body's tissues. In people with Alzheimer's disease, vitamin E might be able to reduce the effects of a protein that's too active in the brain. A study in which many reports from patients with Alzheimer's found that they often had lower levels of vitamin E in their blood [153]. Some tests in patients have suggested that vitamin E, along with an extract from the Ginkgo biloba plant, could be beneficial for brain function. Another study suggested that there is good evidence that vitamin E can help protect against damage caused by certain proteins in the brain of flies [154]. A recent study also suggested that vitamin E could help reduce damage caused by harmful molecules in AD. However, researchers are still studying the positive effects of vitamin E in Alzheimer's, and these studies are ongoing [131].

Vitamin D3

Multi discriminant analysis (MDA) was used by researchers to evaluate the extent of oxidative stress and quantify the activity of the antioxidant enzyme SOD. As expected, injecting A β led to increased MDA levels, an important sign of oxidative stress, and decreased SOD activity. However, when vitamin E and D3 were administered individually or in combination, MDA levels decreased significantly in comparison to the group that received A β treatment. Additionally, the administration of these vitamins enhanced SOD activity compared to the A β -treated group.

The study revealed that injecting A β 1-40 negatively impacted memory and learning in rats during the NOR test [155]. Moreover, A β 1-40 brought about structural changes in the brain. By inducing oxidative stress markers, A β 1-40 caused neurodegeneration in the hippocampus of male rats, resulting in significant neuroinflammation in the central nervous system. The outcomes indicated that long-term vitamin D3 and E administration, either individually or combined, could prevent neuronal changes and neurodegeneration by regulating MDA and SOD levels-critical indicators in Alzheimer's disease (AD). It is widely known that maintaining adequate vitamin levels can help slow down the aging process. Prior research has demonstrated that the human brain possesses a finite amount of antioxidant enzymes, thereby necessitating a diet that promotes the generation of antioxidant molecules. Klotho is one such enzyme that enhances antioxidant molecules within cells [156]. Research indicates that vitamin D3, an intracellular influencer, can boost klotho production and decrease cell oxidative stress. Mice lacking the klotho gene exhibited aging-related traits, highlighting its importance in inhibiting aging-associated conditions like AD. Vitamin D3 can trigger various intracellular pathways, leading to the reduction of oxidative stress. Insufficient amounts of vitamin D in the body can elevate internal oxidative damage and result in a greater incidence of cell death [157]. While vitamin D and E are beneficial for maintaining a healthy brain, it's worth noting that other studies have indicated that high doses of these vitamins might have unintended effects on health [126,131,158].

Caffeine

Caffeine, a commonly ingested alkaloid, has been discovered to hinder the accumulation of A β in laboratory environments. Additionally, it decreases the generation of ROS and increases the levels of SOD in human neuroblastoma cells that are exposed to A β [159]. Moreover, caffeine demonstrates anti-neuroinflammatory properties and reduces the phosphorylation of tau protein in the hippocampus. When ingested in moderate amounts, caffeine hinders the activity of acetylcholinesterase (AChE), resulting in enhanced cognitive function and a decrease in the course of AD [160]. Caffeine, a frequently ingested alkaloid, has been found to impede the buildup of A β in laboratory trials. Additionally, caffeine displays properties that reduce neuroinflammation and decline the phosphorylation of tau proteins in the hippocampus. When ingested in moderate quantities, caffeine hinders the activity of acetylcholinesterase (AChE), resulting in improved cognitive function and a reduction in the advancement of AD [161]. Human research has centered on the antioxidant outcomes of caffeine, which has been linked to the protective influence of coffee against dementia. In order to comprehend the role of caffeine in AD, it is crucial to acknowledge that its impact on the central nervous system (CNS), as a result of regular coffee intake, is mainly accomplished by obstructing

the inhibitory adenosine A1 receptor (A1AR) and the excitatory adenosine A2A receptor (A2AR) [162]. The A1 receptor (A1AR) is a glycoprotein consisting of 326 amino acids. It is highly significant because of its strong attraction to other molecules and its primary occurrence in the central nervous system (CNS), namely in the cortex, thalamus, cerebellum, and other regions within the CNS. In contrast, the A2A receptor (A2AR) is mostly located in central nervous system (CNS) areas that are linked to dopamine, including the striatum, nucleus accumbens, olfactory tubercle, globus pallidus, bulbus olfactorius, and nucleus nervi acustici. All adenosine receptors are classified as members of the G protein-coupled receptor (GPCR) family. Specifically, A1R is categorised under the Gi family, whereas A2AR is categorised under the Gs family. Stimulating A1R on the presynaptic membrane causes adenylyl cyclase activity to be suppressed, resulting in a decrease in cyclic adenosine-3,5 monophosphate (cAMP) levels. This leads to a reduction in calcium ion (Ca²⁺) influx by means of inositol 1,4,5-triphosphate (IP3), ultimately resulting in a decrease in nerve conduction excitability. The A1R receptor functions as a neuroprotective agent in postsynaptic neurons by causing membrane hyperpolarization and decreasing neuronal excitability. Activation of A2AR initiates the protein kinase A pathway, which disrupts nuclear factors-activated- κ B (NF- κ B) and controls the expression of genes. A study has shown that caffeine enhances the activity of Protein Kinase in amyloid precursor protein (APPs), thereby elucidating its neuroprotective impact [163]. A2AR can enhance collagen synthesis, suppress neutrophil peroxidation, and facilitate vasodilation in blood arteries by activating mitogen-activated protein kinases (MAPK) [164]. In Alzheimer's dementia, the hypothesis of adenosine receptor balance suggests that there is a simultaneous reduction in the amount of A1AR? expression and an elevation in A2AR expression. This leads to a disruption in the balance between inhibitory and excitatory processes, ultimately resulting in cognitive dysfunction [165]. Strong evidence from rat models indicates an overexpression of A2AR during the aging process, particularly in cortical and hippocampal areas. Human studies have demonstrated that blocking A2AR with selective antagonists can normalize synaptic and cognitive dysfunctions [166,167]. Caffeine shields against synaptic toxicity induced by A β and safeguards against non-neuronal cells implicated in the advancement of AD by inhibiting A2AR [168]. Neuroinflammation is a critical element in the onset and advancement of AD and the activation of astrocytes and microglia plays essential roles in sustaining the inflammatory process. Activation of A2AR influences both astrocytes as well as microglia, with detrimental impact on neighboring neurons. Activation of microglia which produces inflammatory cytokines as well as neurotoxic substances plays a key role in neuroinflammation.

An additional noteworthy mechanism through which caffeine functions is through its ability to augment the expression of nuclear factor erythroid 2-related factor 2 (Nrf-2). The role of Nrf-2, a transcription factor that possesses a leucine zipper-rich basic motif, in mitigating oxidative stress has garnered considerable attention. Studies over the past decade have highlighted its significance in resisting oxidative damage, as observed in Nrf2 knockout mice that are more susceptible to various pathologies linked to oxidative stress [108,110,169]. Some components of decaffeinated coffee have shown potential benefits in neurodegenerative diseases. Nevertheless, there was no discernible safeguarding impact of decaffeinated coffee on the cognitive performance of elderly subjects. The available evidence from human studies is insufficient to definitively establish the effect of caffeine on the risk of Alzheimer's disease. However, a substantial amount of data from various experimental investigations is increasingly showing the impact of caffeine on cognition and the progression of AD [161,163,167].

Curcumin

Curcumin, the principal component of turmeric spice, was discovered roughly two centuries ago. The substance is obtained from the dehydrated underground stems of the *Curcuma longa* L. plant, which is a member of the Zingiberaceae family. Traditional medicine has employed curcumin to address various ailments, ranging from skin issues, rheumatism, and wounds to conditions like diarrhea, urinary problems, constipation, and inflammation [170]. Furthermore, it has been employed as a dietary supplement and dye in drinks. Curcumin, an aromatic phenolic compound derived from volatile oils, is known for its anti-inflammatory and antioxidant attributes. However, its effectiveness is constrained by challenges like poor absorption, rapid metabolism, limited blood-brain barrier penetration, and poor oral bioavailability. Despite demonstrating therapeutic potential, curcumin's benefits have been more evident in animal studies than in human trials. This discrepancy can be attributed to factors such as the inadequate absorption and metabolism of curcumin in the human body [170,171]. Notably, its low oral bioavailability results in low serum levels after ingestion, potentially leading to insufficient concentrations in the brain. Efforts are being made to overcome this issue by developing novel curcumin formulations, including curcumin-piperidine complexes, curcumin-phospholipid combinations, and polymeric micellar curcumin, to enhance its effectiveness and bioavailability [172]. AD symptoms typically manifest long after the onset of the disease and due to its pharmacodynamic nature, curcumin functions more as a neuroprotective agent than a direct treatment. The mechanisms underlying curcumin's potential role in AD treatment involve inhibiting the formation and aggregation of amyloid-beta ($A\beta$), as well as promoting its clearance [173]. Moreover, curcumin is thought to counteract inflammation, oxidative

damage and apoptosis. The development of new curcumin formulations has shown promise in targeting inflammation, oxidative stress, and apoptosis in brain tissue. The utilization of nanoencapsulated curcumin shows promise in the restoration of memory and reversal of structural alterations in the cortex and hippocampus of rats that have been induced by Streptozotocin. The observed enhancements in memory functions, decreased levels of oxidative stress, normalized activity of AChE, and improvement in neuroinflammatory indicators collectively suggest the potential of nanoencapsulated curcumin to restore brain regions impacted by Streptozotocin-induced damage [172].

Ginger

Ginger, specifically *Zingiber officinale* has been used to help with memory issues in AD. Ginger has some qualities that make it potentially useful for Alzheimer's [174]. It can reduce inflammation and fight harmful molecules in the body. Studies have shown that ginger can boost a substance called nerve growth factor (NGF), which is important for memory [175,176]. In mice, ginger increased NGF levels in the brain, leading to the growth of connections between brain cells [175]. Additionally, ginger seems to block some chemicals that cause inflammation in cells. Animal studies also suggest that ginger can affect certain genes related to inflammation in a good way. Ginger compounds can even cross the protective barrier around the brain, which means they might be able to help with brain diseases like Alzheimer's. Ginger might not only be helpful for Alzheimer's but also for other nervous system problems like brain tumors, strokes, nerve damage, depression, and sleep troubles [174,175,177,178]. It is considered safe by the US Food and Drug Administration (FDA) and can be used as a natural supplement to help with brain disorders. However, there aren't many studies in humans yet, and some of the research involves mixtures of herbs, including ginger. Still, there's promise in using ginger to improve memory and cognitive abilities. The active compounds found in ginger may play a role in controlling various aspects of Alzheimer's disease, such as the response to external stimuli, response to oxidative stress, reactivity to toxic chemicals, lipid metabolism and atherosclerosis, and diabetic cardiomyopathy. In one study, people who took ginger extracts showed better thinking skills, especially at higher doses of 800 mg per day [178].

Fish Oil

Several clinical investigations have demonstrated favourable results in elderly adults with moderate cognitive impairment when they receive supplementation of long-chain omega-3 polyunsaturated fatty acids such as docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) [179]. It's certainly promising to see evidence of a link between higher PUFA levels and improved cognitive performance in older individuals. This aligns with a growing

Table 1. Role of antioxidants in Alzheimer's disease.

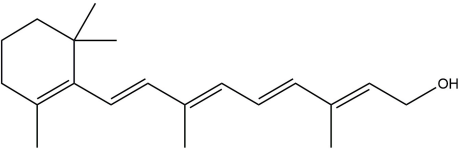
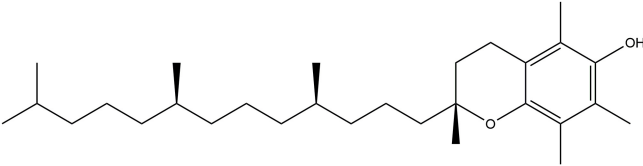
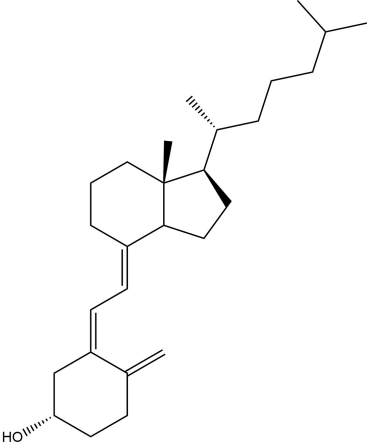
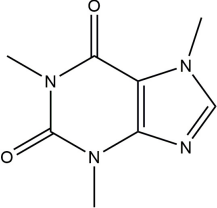
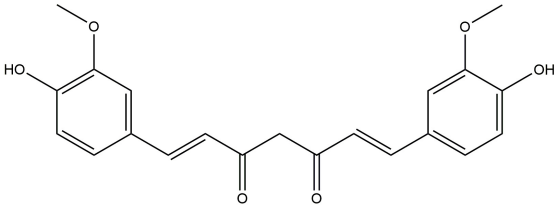
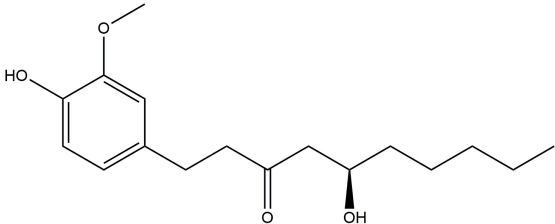
Antioxidants	Structure	Functions	References
Vitamin A		Development of brain cells. Strengthen of long term memory. Protects brain from free radicals. Shows therapeutic efficacy via its anti-amyloid/Tau, antioxidant, and pro-cholinergic effects.	[147]
Vitamin E		Fights against peroxy radicals. Vitamin E prevents the development of hyperphosphorylated tau, a well recognised indicator of Alzheimer's disease, via inhibiting p38MAPK.	[131]
Vitamin D3		Prevents neurodegeneration. Adequate amount helps to slow down ageing process. It induces phagocytosis to remove amyloid plaques and lowers primary cortical neurone cytotoxicity, apoptosis, and inflammatory responses.	[158]
Caffeine		Exerts its neuroprotective effects by binding to A _{2A} receptors, that are triggered by the endogenous nucleoside adenosine.	[184]

Table 1. Continued.

Antioxidants	Structure	Functions	References
Curcumin		It is anti-inflammatory. It increases the phagocytosis of amyloid-beta, effectively clearing them from the brains of patients with AD.	[172]
Ginger		Reduces inflammation. Shows anti-amyloidogenic potential, and cholinesterase inhibition.	[178]
Fish oil		Shows protection against beta-amyloid production, deposition in plaques and cerebral amyloid angiopathy in Alzheimer's disease.	[183]

MAPK, mitogen-activated protein kinase; AD, Alzheimer's disease.

body of research suggesting potential benefits of PUFAs for brain health. Higher concentrations of EPA + DHA have also been linked with a decreased likelihood of developing dementia [180]. In a meta-analysis, the consumption of these fatty acids was shown to have a positive impact. Polyunsaturated fatty acids (PUFAs) are mostly incorporated into phospholipids, sphingolipids, and plasmalogens. They have a significant impact on the physical characteristics of cell membranes, including fluidity, shape, thickness, and permeability. Additionally, they influence the functioning of transmembrane proteins [181]. Research has shown that adding fish oil to the diet can be advantageous for persons suffering from most likely Alzheimer's disease. Supplementing with this substance decreases the amount of lipoperoxides and breakdown products of nitric oxide in the blood, while hovering the ratio of reduced glutathione to oxidised glutathione. The concurrent decrease in the omega-6/omega-3 ratio in erythrocytes alongside increased GSH/GSSG and improved cognitive function adds another layer of complexity and intrigue to this puzzle. It has been observed that patients who maintain a consistent intake of DHA and EPA, both types of PUFAs, experience reduced oxidation of plasma proteins and lipids. This favourable result is significant due to the increased production of ROS linked to AD, which negatively impacts mitochondrial activity, metal equilibrium, and the degradation of antioxidant defences [182]. These factors directly affect neurotransmission and synaptic activity, which eventually leads to cognitive impairment. The production and accumulation of tau proteins that are hyperphosphorylated and amyloid are influenced by the aberrant cellular metabolism seen in AD. These factors can independently intensify mitochondrial dysfunction and further amplify ROS production, thereby maintaining a detrimental cycle that harms cognitive function (Table 1, Ref. [131,147,158,172,178,183,184]). The ingestion of omega-3 polyunsaturated fatty acids in individuals with AD was found to reduce the oxidation of proteins and lipids. This reduction is associated with an increase in catalase activity [183].

5. Conclusion

Alzheimer's disease (AD) is an intricate ailment characterised by the buildup of neurotoxic variants of the A β peptide, which possess the capacity to create amyloid plaques. AD is correlated with a deficiency of the neurotransmitter acetylcholine in the brain, which is connected to modified activity of the enzyme AChE. AChE is accountable for transforming acetylcholine into choline and acetate. Another crucial element in the progression of AD is a disruption in the control of redox metals, resulting in oxidative stress caused by ROS. Multiple indications of oxidative stress have been discovered in the brain affected by AD, such as DNA oxidation products, hydroxyl radical adducts with DNA bases, lipid peroxides, RNS, advanced glycation end products, and other markers. In order to address AD,

contemporary strategies in medicinal chemistry concentrate on developing and studying multifunctional medications that contain features to prevent the aggregation of A β , decrease the activity of AChE, and demonstrate antioxidant and metal-chelating activities. Moreover, the application of herbal treatments, flavonoids, and antioxidants have considerable therapeutic potential. Numerous studies have emphasized the critical role of antioxidants in both the prevention and treatment of various disorders. These drugs have excellent efficacy and often carry minimal risk of adverse consequences. This review study highlights the significant impact of many chemicals with antioxidant qualities, such as vitamin A, vitamin E, vitamin D3, caffeine, curcumin, ginger, and fish oil, in the treatment of Alzheimer's disease (AD). Future research should aim to deepen our understanding of the precise mechanisms by which natural antioxidants exert their neuroprotective effects. This includes elucidating their roles in reducing oxidative stress, modulating amyloid-beta aggregation, and attenuating neuroinflammation. More large-scale, well-designed clinical trials are needed to establish the efficacy and safety of various natural antioxidants in Alzheimer's disease. These studies should focus on long-term outcomes and explore optimal dosages, combinations of antioxidants, and the timing of intervention. The future of Alzheimer's treatment may lie in personalized medicine approaches, where antioxidant therapies are tailored to an individual's genetic makeup, disease stage, and overall health profile. This approach could maximize therapeutic benefits and minimize potential risks. Continued research in these key areas will be essential for developing effective antioxidant-based therapies and ultimately improving the quality of life for individuals affected by this devastating disease.

Abbreviations

AChE, acetylcholinesterase; Ars, adenosine receptors; ATP, adenosine triphosphate; α -TTP, alpha-tocopherol transfer protein; AD, Alzheimer's disease; A β , Amyloid beta; APP, amyloid precursor protein; BACE1, beta-site APP-cleaving enzyme 1; BDNF, brain-derived neurotrophic factor; EOAD, Early-onset Alzheimer's disease; EGCG, Epigallocatechin Gallate; FDA, Food and Drug Administration; HD, Huntington's disease; H₂O₂, hydrogen peroxide; Keap1, Kelch-like ECH-associated protein 1; LOAD, Late-onset Alzheimer's disease; NDs, Neurodegenerative disorders; NFTs, Neurofibrillary tangles; OXPHOS, oxidative phosphorylation; PD, Parkinson's disease; PTEN, Phosphatase and tensin homolog; PUFA, polyunsaturated fatty acid; RNS, reactive nitrogen species; sAPP α , soluble amyloid precursor protein alpha; TBARS, thiobarbituric acid reactive substances.

Author Contributions

RAN, MNM, IAM, RB, FMA, MA, MAM, ASA, WFA, AH, TG, BP, MPS, GTS and SKS have significantly

contributed to the idea and design of the project. MAM, ASA, WFA, AH and TG performed the literature review and wrote sections (1-3). MNM designed the diagram and the illustrations. RAN, GTS and IAM designed the structures and their illustrations. RB, FMA, MA wrote section “4”. BP, MPS, and SKS critically authored and reviewed the texts for significant intellectual substance and approved the final version. All authors have adequately contributed to the work to assume public responsibility for relevant sections of the material and have consented to be responsible for all facets of the work, ensuring that inquiries about its accuracy or integrity are addressed. All authors made contributions to the manuscript’s editorial revisions. All authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

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Conflict of Interest

The authors declare no conflict of interest.

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