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Review Article

Carotenoids and their formulation supplements in Alzheimer's disease

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ABSTRACT

Alzheimer's disease is a type of neurodegenerative disease that is mistakenly confused with aging and is oftentimes misdiagnosed. One of its main characteristics is the loss of nerve connections and functioning neurons in the cerebral cortex and some subcortical areas. The sheer number of people affected by neurodegenerative diseases globally is startling, but this is at the top of the list. Called memory loss disorder, it starts slowly and gets worse over the years. This seemingly incurable and severely crippling neurodegenerative dementing disorder affects the hippocampus. Changes in this region's physio-anatomical function lead to inability to form new memory nerves, or to entire memory loss that is linked to brain impairment. The pathophysiology of Alzheimer's disease has been linked to protein misfolding, where folded amyloid beta proteins in neurons and brain tissues are replaced by larger pathogenic proteins known to aggregate. Clinically recognized early-stage symptoms include language issues, apraxia, challenges with perceiving, writing, dressing, other motor skills, and difficulty with movement coordination. Diagnostic criteria have identified middle-stage symptoms as speech difficulties in the patient, most notably paraphasia, inability to identify family members, unguarded aggression, lack of civility when urinating, and other neuropsychiatric-behavioral changes. Severe symptoms include total dependence on the caregiver and total loss of speech. Even though there are no proven treatments, new research highlights the possible roles that certain dietary components, most especially, carotenoids may play in both prevention and management. With recent advances in biotechnology, genome editing, and AI-driven precise and personalized medicine, there is hope that the absorption, distribution, metabolism, and excretion of carotenoid supplements can be optimized for increased bioavailability along the gut-brain axis and efficient blood-brain barrier crossing. The emerging possibilities present a strong opportunity to enhance the therapeutic impact of carotenoids on Alzheimer's disease.

KEYWORDS: Alzheimer's, Aggregates, Carotenoids, Neurodegeneration, Supplements

1. Introduction

Alzheimer's disease is a type of neurodegenerative disease that people mistakenly confuse to be aging, due to some similar features and processes shared with aging and about 20% are diagnosed wrongly [1,2]. Loss of functional neurons and nerve synapses within the brain's cerebral cortex and extending to some part of the subcortical are major characteristic features of this disease [3,4]. Alzheimer's disease is the most common and rampant neurodegenerative disease in terms of the number of sufferers in the world. The disease was named after the scientists, who first gave a public description of this clinical condition back in 1906 [5]. Basically referred to memory loss disorder, the disease shows a slow onset and continues to worsen progressively over years. In fact, this disease accounted for over 60% of medical cases reported and linked to dementia worldwide [6]. The disease primarily affects the part of the brain that functions to memory which is known as the hippocampus and causes alteration in the physio-anatomical function of this region resulting in loss of memory attributed to brain impairment. Although memory loss is the most paramount and most identifiable symptom in Alzheimer's disease, language problems, apraxia, difficulties in perception, writing, dressing, and other motor activities as well as movement coordination are clinically identified as early-stage symptoms [7]. Difficulties in speech, most notably paraphasia, failure to recognize relatives, untailored aggressiveness, loss of courtesy in urination, and other neuropsychiatric-behavioral alterations have been identified diagnostically as middle-stage symptoms while at the severe stage, complete reliance on the caregiver and absolute loss of speech exist [8]. The pathogenesis of this disease has been attributed to protein misfolding due to significant aggregation replacing folded amyloid beta proteins in neurons and brain tissues. In a homeostatic state, the amyloid beta proteins are sub-part of a transmembrane protein called amyloid beta precursor which functions upon transport via neuron's membrane to promote growth and repair of nerve cell, but when largely gathered thus ravel them to fold randomly so as to associate together leading to abnormal folding within the cell as neurofibrillary tangles and outside the cell as amyloid plaques and Tau proteins [9]. These plaques are insoluble deposits which give it the name proteinopathy. Also, the Tau proteins aid the transport of nutrients, and other vital nutrients are further subjected to phosphorylation leading to the formation of paired thread-like structures called neurofibrillary tangles [10]. All these result in neuronal toxicity, then coupled with oxidative stress, decreased protein clearances of the system, and neuro-inflammation response in eliminating these plagues results in neuronal functions loss and death, disruption of calcium homeostasis, induction of apoptosis, mitochondria malfunctioning and energy depletion [11]. The etiology of this disease is also multifactorial as this is linked to genetic and environmental factors. In terms of genetics, Alzheimer's disease can be inherited when any of these autosomal dominant genes: APP, PSEN1/2 which codes for amyloid precursor proteins and presenilins are inherited [12] or when there is a mutation of gene APOE£4 which codes for apolipoproteins E [13]. Environmental factors including exposure to traffic exhaust and burning, excessive consumption of alcohol, poor sleeping lifestyle, and high cholesterol intake are risk factors that enhance the development of Alzheimer's disease. Alzheimer's disease is also being managed medically as there is no true cure for it. Medical interventions made so far on this disease were to reduce the onset and progression of the disease. Such as medications that could enhance memory and cognitive function including tacrine (an acetylcholinesterase inhibitor) and memantine which function as N-Methyl-D-aspartate receptor antagonists [14], as well as other drugs that could lower depression, inflammation, hypertension, and cholesterol level are usually employed depending on the pronounce symptom in individuals [15, 16]. Also, physical exercise, educational engagement, abstinent from smoking, adequate sleep, and living less stressful are lifestyle changes that could help in managing this disease condition. Carotenoids represent a family of naturally occurring pigments prevalent in plants, algae, and specific bacterial species. These compounds are pivotal for the vivid hues observed in various fruits and vegetables like carrots, tomatoes, and spinach. Beyond their role in coloration, carotenoids are crucial for plant vitality, shielding them from light-induced harm and contributing to the process of photosynthesis. With an excess of 600 diverse carotenoid variations, they segregate into two primary categories: carotenes, comprising hydrocarbons, and xanthophylls, which integrate oxygen atoms. Certain carotenoids, like beta-carotene, can undergo conversion into vitamin A within the body. Vitamin A stands as a critical element for vision, immune fortification, and cellular proliferation. Carotenoids boast an array of potential health advantages encompassing the reduction of chronic ailments such as heart disease, stroke, cancer, and age-related macular degeneration. Additionally, specific carotenoids, such as lutein and zeaxanthin, concentrated notably in the macula—the central vision-responsible part of the eye—may aid in safeguarding it from age-related macular degeneration. Their inherent antioxidant and anti-inflammatory traits potentially contribute to enhancing the immune system which have been explored as neuroprotective actions in suppressing AD symptoms [17, 18]. This chapter focuses on the major hallmarks of AD and the mechanisms of carotenoids and their formulation supplements in mitigating each hallmark of AD.

2. Pathogenesis of Alzheimer's disease and dementia

Understanding the key players in the pathogenesis of Alzheimer's disease and dementia is essential to providing therapeutic approach(es) that could halt/reverse/retard the progression of the disease. This section provides as overview of the major factors in Alzheimer's disease and dementiaincluding neuroinflammation, oxidative stress, cholinergic system. The crosslink between them was discussed and the later part discussed the role of carotenoids and how each of these carotenoids with neuroprotective properties was able to mitigate these hallmarks.

2.1. Neuroinflammation and its mechanism in Alzheimer's disease

Inflammation is a key process that playas crucial part in the body's defense mechanism against injury and infections. Recognition and removal of harmful xenobiotic and foreign stimuli by the immune system in the body constitutes an inflammatory process [19]. The multiple physiology of this process is felt when halted or absent, most especially in wound healing, infection, and clearing out of abnormal proteins, necrotic cells, and damaged tissue, as this clearing process becomes complicated. In fact, too little or prolonged inflammation is complicated, as these can lead to progressive tissue destruction and diseases like arthritis, dermatitis, cystitis, heart disease, cancer, stroke, and others [20]. Such is a typical case in most neurodegenerative diseases such as Alzheimer's disease. The physiological process could be acute and chronic depending on the duration and onset, and these can occur in many organs and tissues ofthe body. Neuronal inflammation which is termed neuroinflammation is a typical example inflammation process occurring in the brain, spinal cords, and nerve cells. Inflammation within the brain has dual physiology as it can play a crucial neuroprotective role during an acute-phase response and could be detrimental and complicated if occurred as a result of a chronic response [19, 21]. Neuroinflammation is one of the most common pathological mechanisms associated with Alzheimer's disease (AD) and other neurodegenerative diseases [2,4]. AD developed due to chronic inflammatory responses within some regionsof the brain because this neurodegenerative condition has been reported to exhibit slow onset and progressive pathogenesis. Progressive diminishing in active memory and memorial retrieval, and diminishing in learning, language, and cognitive function were commonly reported most profound associated features of AD [19]. Although an extracellular deposit of amyloid beta $\alpha\beta$ and tau proteins and intracellular deposit of tau protein as neurofibrillary tangles (NFTs) are the pathological hallmarks implicated in the development of AD [23]. Pathological evidence of these was reported in a postmortem brain examination, which showed significant Aβ depositions in certain brain regions such as entorhinal cortex layer II, the nucleus basalis, the frontal cortex, and other cortical/subcortical regions for AD patients [24]. All these results in detectable neuronal losses in these multiple regions stated [24, 25]. However, Inflammation is one of the principal molecular mechanisms among many other molecular mechanisms interrelated in complex vicious circles which eventually results in neuronal cell dysfunction and death [22]. Among these includes oxidative injury, impaired bioenergetics and mitochondrial dysfunctions, and excite-toxicity [22, 24]. Inflammation does not only play a role in disease pathogenesis but also playsa crucial role in the diseased progressive, as the neuroinflammatory cascade processes induce, pronounce, and exacerbateother associated pathological mechanisms implicated in the disease's etiology. Therefore, neuroinflammation plays an active and fundamental role inthe development of AD as evidenced by overexpression of pro-inflammatory markers which further triggers increased accumulation of Aβ peptides, the activation of astrocytes and microglial cells [26]. Irrespective of the cause of αβ-amyloid deposit whether by genetic mutation of the genes encoding amyloid protein precursor (APP), presenilin 1 & 2(PSEN1/2), or exposure to neurotoxicants, leading to improper cleavage of the amyloid precursor protein (APP) causing aggregation of αβ monomers as oligomeric αβ fibrils and plaques, aggregation of the αβ plaques causes recruitment of microglia which interact and binds to the soluble amyloid Aβ oligomers and Aβ fibrils through the cell-surface receptors to any of the following receptors Toll-like receptors (TLR-2,4,6 & 9), clusterof differentiation (CD) receptors (CD47, CD14, CD36, α6β1 integrin, CD47) by ligation process as clearance mechanism for the plaque [27]. The recruited microglia begin to encircle or engulf Aβ fibrils by phagocytosis mechanism. This interaction leads to the production of pro-inflammatory cytokines and chemokines such as IL-2, IL-6, and IL-1β, tumor necrosis factor (TNF-α), nitric oxides, and with free radicals' generations to enhance the clearance process via endo-lysosomal pathway but due to non-soluble nature of the plaque fibril, this result in compromised microglial function as there is inefficient clearance capacity of Aβ [27,28]. The overall effect is further increased Aβ deposition and cytokine concentrations and downregulation in the expression of Aβ phagocytosis receptors, evidence of these was shown by the detection of Pittsburgh compound B (PiB)-PET in the brains of AD experimental animal model [29]. Next to activated microglia is a complex and multiple-stage pathological reaction leading to reactive astrogliosis or glial scar around the amyloid plague. In AD, hypertrophic reactive astrocytes accumulate around senile plaques causing extension of the fibril aggregation, evidence of this was reported to surface in post-mortem human tissue of Alzheimer's disease patients [30-32]. During this, the glial cell gets activated through the co-interaction of the glial fibrillary acidic proteins, and vimentin results in the formation of astrocyte-specific intermediate filament protein intermediate inside the astrocytic process causing further extension of astrocytic processes around aggregated plague. These astrocytesalso inducethe production of interleukins, nitric oxide, cytokines, interleukins, nitric oxide, and other potentially cytotoxic molecules due to aggregation of aberrant Aβ amyloid proteins [33], thus aggravating the neuroinflammatory responses further. However, various kinds of carotenoids have been demonstrated to mitigate neuroinflammation in the different models of AD using different approaches and mechanisms, this will be discussed in detail later in this chapter.

2.2. Oxidative stress in Alzheimer's Disease (AD)

The discovery of oxidative stress (OS) over many decades as one of the contributors to the molecular pathogenesis of many chronic and deadly diseases has created a new frontier in studying of molecular mechanism of diseases and in treatment administration [2,4]. AD, a disease characterized by memory impairment and dementia due to loss of functional neuronal as a deposition of extracellular senile plaques, neurofibrillary tangles (NFTs), and neurodegeneration [34]. Avalanche of research evidence via molecular pathological findings have linked OS to AD [35,36]. The reportshave shown that OS contributes to the etiology and molecular pathogenesis of AD [2,4,35,36]. Disruption of metabolic balance between the amount of free radical and reactive oxygen species (ROS) generated due to metabolism and the body cell antioxidant system result in oxidative stress in favour of the former [37-40]. Production of free radicals and ROS within the cell during metabolism is inevitable due to cellular exposure to radiation, pollutants from environment, and toxins; their participation in process of oxidative phosphorylation and also these energetic species form integral part of cellular defense and in detoxification of xenobiotic, but when the quenching actions of cell against the reactive species through the use of antioxidant is lower than their production, then the excess attacked cellular macromolecules, leading to diseases conditions[37-40]. This is a similar mechanism replicated in AD and any other diseases implicated with OS [2,4]. The chemistry behind the attack of free radicals and ROS is due to the fact that they contain unpaired electrons in their atomic orbital which makes them highly unstable and enables them to partake in oxidation and reduction

(REDOX) reactions with cellular macromolecules such as DNA, proteins, lipids, and other structural macromolecules, thus causing cellular injury. Generally, ROS constitutes both radical and non-radical oxygen species like superoxide radical anion (O2-.), peroxynitrite (ONOO-), nitric oxide (NO), hydrogen peroxide (H2O2), and hydroxyl radical (HO) which all produced as when oxygen is subjected to partial reduction process [36]. Some of these species have been reported to cause oxidative cellular injury in neuronal brain cell AD patients thus implicating their contribution to AD development and in progression of this pathological condition. The human brain cell is susceptible to oxidative attack by free radicals and ROS due to its high demand for molecular oxygen for metabolism activity. Brain cells use glucose mainly as metabolic fuel material which is broken down by glycolysis to generate ATP via oxidative phosphorylation for neuronal cells functioning. Also, the brain cells contained high levels of polyunsaturated fatty acids which are highly susceptible to oxidative attacks by free radicals and ROS, and little amount of ROS and free radicals were also formed via redox activity of some transition metal ions present in the neuronal. These coupled with the low antioxidant capacity of the brain result in homeostatic imbalance, therefore it is crucial to combat this attack through dietary supply of antioxidant molecules [2,4,41].

2.2.1. Role of Oxidative Stress in development and progression of AD

Amyloid deposition via abnormal Aβ accumulation, tau hyperphosphorylation, neurofibrillary tangles (NFTs) formation and neurodegeneration leading to memory impairment and dementia were pathological characteristic feature of AD. Oxidative stress, impaired bioenergetics and mitochondrial dysfunction, apoptosis, excitotoxicity, cellular macromolecules (DNA, protein and lipid) and membrane damage were part of the molecular pathological mechanisms leading to expression of the above stated pathological characteristic features[42]. Among all this disease molecular mechanisms, oxidative stress is known to be the hall mark of all these molecular pathological mechanisms which lead to development of AD. ROS is known to be generated as part of intermediate products in metabolic pathways and through redox reaction in the electron transport chain process. Also, low amount of these ROS is essential for normal physiological functioning of cells such as in detoxification and cell defense against pathogens, but when their production rate is higher than cell antioxidant capacity, then they escape and attack the cell and its structural component leading to diseased state. This is typical case in AD development and progression. To better understand the mechanism by which OS contribute to AD development and progression would be discussed under the following headings:

2.2.2. Clearance and production aggregation Aβ proteins

Clinical study and postmortem brains examination has shown a significant Aβ depositions in certain brain regions of AD patients [43]. Up-regulation of both tau phosphorylation and Aβ production have also been reported to also caused by ROS upon inducing oxidative stress, because increased OS biomarker induces generation of advanced glycation end products (AGEs) which binds to receptor for advanced glycation end products (RAGE) causing transcription and synthesis of BACE1 via activation of the NF-κB signaling. This BACE1 now enhances Aβ production. Although amyloid deposition can also occur through genetic mutation of ApoEA or TREM2 genes, cholesterol buildup or infection, and inflammatory diseases. Irrespective of the causes, the brain cell can also induce ROS as a clearance mechanism to clear off these aggregated proteins, but excessive generation results in unregulated damage to the neuronal cell membrane and structural macromolecules (DNA, lipids, and proteins), which eventually leads to blockage of the dendrites, synaptic membrane, and axon leading loss of function of neuronal cell and death [41,44].

2.2.3. Oxidation of cellular macromolecules

Cellular macromolecules such as DNA, proteins, and lipids are susceptible to oxidative attack if they exist in an oxidative environment. In AD, ROS generated via routes mentioned above can oxidize proteins by carbonization of protein via direct oxidation of Lys, Arg, Pro, and Thr residues and leading to the destruction of the 3D of structure of cellular proteins which is important for protein functioning. These carbonylated protein products are also used as clinical biomarkers of the measurement of protein carbonylation and the extent of this damage in AD [42, 45]. ROS can also induce lipid peroxidation of neuronal cell membranes and other lipid component leading to the generation of lipid peroxidation products. Evidence of this is shown by an increase in cellular levels of 4-hydroxy-2,3-nonenal (HNE), acrolein, malondialdehyde, and F2-isoprostanes in AD brains and these are used in clinical biomarkers of AD [46,47]. Peroxidation occurs by oxidation of the double bonds in polyunsaturated neuronal lipid and these lipid peroxidation products are extremely reactive, being able to stimulate phosphorylation and dysfunction of tau, disruption of intracellular Ca^{2+} signaling pathway, and induction of an apoptotic cascade leading to cellular toxicity [42]. The mitochondrial and nuclear DNA are also susceptible to ROS oxidative through nitration, carbonylation, and hydroxylation, leading to DNA crosslinking with itself or proteins, and these cross-linked product exhibits mutagenic behavior. Evidence of this nucleotide damage in AD is reflected by the presence of hydroxydeoxyguanine (8–OHdG) co-localizing with Aβ and p-tau plague in some parts of the brain like frontal lobes and temporal [41]. Additionally, the clinical pathological study also evident the expression of Advanced glycation end products (AGEs) in the plague extracellularly in AD [45], which is formed by spontaneous condensation of ketone or aldehyde groups of sugars with a free amino acid group of proteins non enzymatically as an oxidative. Immunohistochemical studies have also demonstrated the presence of AGEs in association with two major proteins of AD, Aβ66, and MAP-tau [45]. The cumulative effect of ROS attacks on cellular macromolecules via oxidation in the neuronal cell results in excitotoxicity, loss of viable cells, and death.

2.2.4. Fenton redox reaction induced by metal ions

Disease progression of AD has also been linked to ROS production via the Fenton redox reaction within the neuronal cell. Some metallic ions are structural components of metalloproteins, complexes in the electron transport chains, and enzymes. Examples includes Cu^{2+}, Fe^{2+} and Zn^{2+}. Biomedical reports showed 3-fold increase in the level of Cu^{2+}, Fe^{2+} and Zn^{2+} in the neuronal cells of AD patients when compared with that of healthy individuals. The metallic ion can participate in Fenton-Haber reaction via oxidation to generated ROS such as hydroxyl radical upon binding to the N-terminal hydrophilic ends of Aβ monomers peptides and this binding causes the precipitation of proteins making aggregation into neurotoxic oligomers which form plaques. Likewise, they bind to tau proteins enhancing their phosphorylation leading to fibrillation and plague formation in the neuronal cells [48, 49].

2.2.5. Mitochondrial dysfunction and impaired bioenergetics

Exposure to ROS at an acute level causes mitochondrial permeability transition (MPT), leading to elevated level of phosphate and decreased level of adenine nucleotide, this is followed by uncoupling of oxidative phosphorylation, cytotoxicity, and the neuronal cells is forced to undergo necrosis and apoptosis as it releases the cytochrome C and apoptosis-inducing factor component [50]. Also, ROS causes oxidation of the carbonyl group of the amino acids' residues of ETC which alters their conformational structure which is crucial for their functionality, evidence of this was reported for lipo-oxidation and nitration of ATP-synthase sub-units in the hippocampus and parietal cortex of AD patients. This led to compromised oxidative phosphorylation as indicated by decreased ATP production, elevated oxidative stress, and ultimately cell death and mild cognitive impairment [51].

2.3. Cholinergic system in AD

Crucial physiological and psychological functions like sensory information, cognitive skill and control, learning, memory, thinking, sleep, attention, stress cycle and response as well as wakefulness were integral functions of the cholinergic system (CS) [52]. This system basically transducessignals via the central Nervous System through the cholinergic signaling molecule called acetylcholine. Deficit in physiological, biochemical, and structural roles of the CS in the form of cholinergic atrophy, synaptic defect, loss or depletion leads to cognitive decline, progressive memory loss, and other pathological symptoms associated with AD [53, 54]. Aside from these physiological and psychological roles, the CS has also been reported to play a crucial role in synaptic plasticity and regulation, neuronal protection and differentiation, neurogenesis control, and neuronal differentiation which are significant for the central nervous system processes [55]. Alteration in one or more of these physiological functions of the cholinergic system has been linked to neuronal abnormality and decline which accelerates the onset of AD pathogenesis. These abnormal central cholinergic changes have also been reported to induce and exacerbate other pathological phenomena such as abnormal phosphorylation of tau protein, nerve cell inflammation, cell apoptosis, neurotransmitter and neuro-hormone system imbalance in AD.

2.3.1. Cholinergic System

The cholinergic system comprises the acetylcholine (acting as a neurotransmitter molecule), the acetylcholine or cholinergic receptors (AChRs) which bind to the neurotransmitter, and the enzymes involved in signal transduction which are choline acetyltransferase and choline acetylcholinesterase. The system synthesizes acetylcholine using choline, Acetyl-CoA, and ATP catalyzed by choline acetyltransferase, while it is degraded by acetylcholinesterase. These two reactions are key components in signal transduction via synaptic, parasympathetic, and sympathetic processes. Although, muscarinic AChRs (mAChRs) and nicotinic AChRs are the two types of ACh receptors, mAChRs function at the CNC andneuromuscular and get triggered by intracellular G-Proteins activity while nicotinic AChRs works for peripheral system and CNS and mediated by ion influx [54-56]. This cholinergic system is the basic functionality of the cholinergic neuron, which is widely distributed in some parts of the brain and CNS as a whole. The basal forebrain region whose cholinergic neuron cluster forms a system projection thatlinks the cingulate, occipital, temporal parietal, and frontal cortices. Most importantly, the nucleus basalis of Meynert is richly endowed with this cholinergic neuronal system, and this basal forebrain cholinergic neurons define the process of learning, memory, cognitive function, and temperature and sleep control [57]. The cellular degradation leading to degeneration of this basal cholinergic system, and specifically the deep part of the nucleus of basalis Meynerthas been implicated in the degenerative pathology expressed in AD and for its progression [58].

2.3.2. Cholinergic system defect as mean in the pathogenesis of AD

Early 1990s, the dysfunction in the cholinergic system was used as the molecular mechanism behind the pathogenesis of AD, the discovery was put forward as “Cholinergic Hypothesis of Alzheimer’s Disease’. Basal forebrain cholinergic neurotransmission dysregulation and changes in the homeostatic levels of cholinergic-associated biomarkers like ChAT, choline, and Ach were linked to the deficit in cognitive physiology in AD. Though the hypothesis was challenged, further studies now clarify that cholinergic system deficit and other pathological mechanisms result in AD [54,59]. As of now, aggregation and deposition of amyloid beta and tau are known to be the main surfaced neuronal pathological characteristic features associated with progressive neuron loss in the brain of AD. Aside these, abnormal protein dynamism, mitochondrial dysfunction, neuro-inflammation, oxidative injury, and impaired bioenergetics were some notable pathological mechanisms contributing to the development and progression of this disorder [60]. However, available research has also pointed out defects or dysfunction in the cholinergic system as one of the main pathological mechanisms involved in the onset and development of the disease as it promotes changes in amyloid precursor protein (APP) metabolism and tau phosphorylation, leading to neurotoxicity, neuroinflammation, and neuronal death [54, 61]. For better understanding, the causes of the defect in the cholinergic system, how it is interlinked and exacerbate other pathological mechanism will be discussed below.

2.3.3. Amyloid protein interaction with the cholinergic system

Amyloid protein and neurofibrillary tangles (NTF) are the most common pathological hallmarks of AD. Amyloid beta protein formation could occur due to genetic mutation of amyloid protein precursor (APP) or presenilin 1 & 2 (PSEN1/2), or apolipoprotein E (APOE-e4) genes; environmental or occupational exposure to neurotoxicants, leading to aggregation of αβ monomers as oligomeric αβ fibrils and plaques while dysregulation dephosphorylation and phosphorylation or Aβ-protein formation causes phosphorylation of tau proteins which aggregates as well [62, 63]. Irrespective of the causes, studies have shown that Aβ binds to alpha 7 nicotinic AChRs with high affinity and decreases the activity, by reducing the ACh synthesis in the neurons; impaired signal transduction by decreasing the number of neurotransmitters available for binding to the receptor; increasing AChE activity and as well decrease the choline acetyltransferase activity as reported [64], in some brain parts like prefrontal cortex, prefrontal cortex and hippocampus in AD experimental animals injected with Aβ-protein. The basal forebrain cholinergic neuron dysfunction also enhances the activation of Rab5 which causes endocytosis and endosomal/lysosomal pathways disruption leading to axon transport and endosomal enlargement. Significant increase in apoptosis, mitochondrial dysfunction, and impaired bioenergetics were also reported in another study due to coupled effects of amyloid protein aggregation and dysfunction of the cholinergic system in all brain regions of mice [64-66].

2.3.4. Reduction in the functional cholinergic system due to genetic defects

Reduction in the distribution of the number of nicotinic and muscarinic receptors in basal forebrain cholinergic neurons which are two types of receptors for acetylcholine widely distributed within the brain. This is another principal factor contributing to the defect in cholinergic receptors and memory decline in AD. Five sub-units of muscarinic receptors (mAchR) have been identified and tagged as M1, M2, M3, M4, and M5 which all play a role in signal transduction through the G-proteins while about twelve sub-units of nicotinic receptors nAchR have been identified, tagged as subunits α2 to α7, α9, α10 and β2 to β10, but among all, α4β2 nAchRs and α7 nAchRs are widely distributed in the brain of AD patients and their reduction have been linked with AD pathogenesis [67,68]. Results from both postmortem studies of AD patients with advanced stage AD and that cohort of patients with mild cases of Alzheimer's dementia confirmed a decrease in the expression of α4β2 nAchRsand α7 nAchRs Alzheimer's dementia in various brain parts of the basal forebrain, the cortex and hippocampus and the basal forebrain. Genetic polymorphism has been reported to account for the decrease in the expression of the loss in functional α4β2 nAchRs and α7 nAchRs in the brain. This was revealed via genetic analysis done using single nucleotide polymorphism of the nAChRs genes (CHRNA7, CHRNA4, and CHRNB2 genes in AD patients and controls, result shows that rs4779978 and rs1827294 on CHRNA7, rs1044394 on CHRNA4 and rs1127314 on CHRNB2 were significant statistically when compared with control [69,70]. These results validated earlier made by some researchers, in that reduction in neuronal cholinergic transmission in AD patients due to loss ofAchRs. In fact, the loss was estimated to be around 30-40% for alpha-4-containing receptors and 17% to 50% loss for alpha-7-containing receptors of the loss of alpha-4-containing receptors in AD patients as compared to normal healthy patients [71,72]. Therefore, it can be establishedthat the decline in signal transduction via cholinergic receptors in AD patients is linked with loss of cognitive, and behavioral attention deficit and impairment in attention performance and gradual loss of functional nAchRs in AD.However, other histochemical and brain imaging studies of autopsy of AD brain tissue of patients explained further that the reduction in nicotinic cholinergic signal transduction and excitation may not only impair the postsynaptic depolarization but can as well induce neurotransmitter release by the presynaptic system and Ca2+-dependent intracellular signaling, thus altering mitochondrial functions, cellular bioenergetics, and neuronal death at final stage, this evidence create link between defective cholinergic system, impaired Ca2+ homeostasis and mitochondrial dysfunction [54,73].

2.3.5. Oxidative stress and cholinergic system defect

Oxidative stress is another pathophysiological factor that has been reported to cause destruction of the cholinergic system. In response to the cell to clear off the amyloid plague, free radicals and ROS are generated by phagocytic cell or liposomal bodies, which interact with thenAChRs- beta-amyloid binding complexes leading to induce lipid peroxidation and further free radical formation which attack the neuronal cell membrane, its receptor (in which cholinergic receptor is part of) and receptor-neurotransmitter complexes, thus impair cholinergic system function. A report from another study shows pretreatment with an antioxidant ameliorates this cholinergic system dysfunction [72], this result confirmed the role of oxidative effect in cholinergic system dysfunction.

2.3.6. Blockage of nAChR proteins transport

The tau proteins are known to be involved in the process of intracellular transport of proteins, but these proteins become hyperphosphorylated and aggregated to form NFTs protein by hyperphosphorylation of tau, the aggregated protein make them lose their structural and functionality, hence their transport into cell membrane are blocked by both the amyloid plague and NFTs proteins, leading to impaired functionality as there is overall loss of nAChR expression due to an insufficient or hindrance in their transport of upon biosynthesis.

3. Role of selected carotenoids in mitigating the pathogenesis of Alzheimer's disease and dementia

3.1. Crocetin

Crocetin is an apo-carotenoids with neuronal heath beneficial effects. Apo-carotenoids are carotenoids are derived by enzymatic or nonenzymatic process through oxidative cleavage of carbon-carbon double bonds in the carotenoid's backbone. The class of carotenoids play crucial regulatory as signaling molecules, growth stimulator and inhibitor and as defense molecules in plant. Classical examples of apo-carotenoids are crocetin and crocin. Crocetin and crocin roles in AD pathogenesis had been elucidated [74]. Crocetin is a dicarboxylic acid containing apocarotenoid which is also derived from saffron with molecular formula C20H24O4. Both in vitro, in vivo, and human studies had affirmed anti-inflammatory, free radical and ROS scavenging potential and neuronal protective potentials of crocetin in ameliorating AD pathogenesis [75,76]. For example, in vitro study was carried out using APP induced AD in SH-SY5Y cell lines treated with 0.1 μmol-1 mmol dose of trans-crocin 4 and trans-crocetin for about 24-72 hrs to examined their effect on amyloidogenic pathway. the results obtained showed trans-crocin 4significantlymodulated amyloidogenic pathway by increasing the level of γ-secretase, decreasing the level of amyloid precursor protein-C99 (APP-C99) and β-secretase whose combined effect resulted in production of toxic Aβ peptides in AD [77]. Nevertheless, trans-crocetin reduced the level of both β and γ secretase enzyme and the aggregated amyloid-β precursor protein (AβPP), but when both transcrocetin 4 and trans-crocinwere used, reduction in the level total tau and its phosphorylated form as well as decreased in level of active enzymes GSK-3β and ERK1/2 kinases were observed in the same study. Therefore, it can be affirmed that these two apocarotenoids can biochemically modulated the molecular pathways implicated to enhanced the development [78]. With respect to the use of this apocarotenoid supplements, one study documented the use of crocetin supplement at dose of 10 μmol of the supplement inclusion complex made by encapsulating crocetin with γ-cyclodextrin in an 7PA2 AD cell line. Thisresulted in the down regulation of Aβ protein in neuronal cell and strong protection against H2O2 generation which promotes and induces neuronal cell death in the AD [77]. Similar to other carotenoids, the efficacy of crocetin is also a dose dependent. This evidence was affirmed in an in vitro study using CD14+ monocytes expressing Aβ proteins isolated from AD patients. Treatments were done for this cell and that of normal cells isolated from healthy individuals as control at varying doses ranging from 5 to 150 μM of trans-crocetin for different time ranges of about 24 to 120 hours. Results obtained affirmed that trans-crocetin administration enhanced the breaking down of Aβ42 proteins in AD monocytes and this effect was reported to be in a dose-dependent pattern [79]. As suggested, the mechanism might probably be through the up-regulation of the lysosomal enzyme called protease cathepsin B which helped in the degradation of the amyloid proteins, making it exhibit an anti-amylogenic effect. However, the amyloid protein clearance mechanism of crocetin has been linked with the ability to enhancethe autophagy process in neuronal cells with aggregated Aβ42 proteins. This study was conducted by treatment of crocetin supplement at a concentration ranging from 3.12–50 μM for 12hrs in a transgenic N9 cell line which expresses Aβ42 as implicated in AD pathogenesis. Activation of serine/threonine kinase 11 (STK11/LKB1) which mediates the activation of AMP-activated protein kinase (AMPK) and its pathway which is one of the activators of autophagy process which help in the clearance of this amyloid protein [80]. In a similar effect, treatment of wild-type C57BL/6 mice with 10 mg/kg of crocetin for 30 days affirmed this clearance of crocetin on accumulated Amyloid protein and further established that crocetin can cross the BBB for easy translocation between the neuronal cell in the hippocampus of the brain [80]. Lastly, autophagy effect through induction of autophagy-mediated AMPK pathway and amyloid proteins clearance, coupled with suppression of the NF-κB and P53 expression and reduction in recruitment of inflammatory cytokine level in the hippocampus of the5× FAD transgenic mice and APP751 Swedish mutant were reported [80].

3.2. Crocin

Crocin is a water soluble carotenoids which is an ester of crocetin. The chemical name of crocin is 8′diapocarotene-8′8-dioic acid while its molecular formula is $C_{44}H_{64}O_{24}$. This compound is responsible for the pigmentation of stigma in plant like Crocussativus L. The presence of this chemical in plant Saffron has been attributed to it pharmacological activity. Available research evidence has shown that Crocin exhibited anticancer, antioxidant, anti-inflammatory, hypolipidemic, hypotensive, antidiabetic and anticonvulsant effects [74]. Also epidemiological and in-vivo studies have revealed the protective role of Crocin against clinical pathological features and symptoms in AD [74,81]. Interestingly, one among these in vitro studies was conducted using STZ-induced AD mice model treated with 100mg/kg supplement of crocin for about 21days, results obtained showed that treatment of the crocin supplement significantly decreased the level of lipid peroxidation product called malondialdehyde; increased the level of total thiol content, and enhanced the enzymatic activity of the glutathione peroxidase, thus it helped to reduce the level of oxidative stress which accounted for its enhanced cognitive performance. The research report showed that crocin supplement intake can serves as reposing drug to ameliorate the memory and learning impairment associated with AD [82]. Likewise, the use of this crocin supplement have also been reported to help reduced the level of another lipid oxidation by product called acrolein, which has been linked to caused induction of oxidative stress-mediated pathogenesis of AD and aging of brain [82]. To further explore the protective role of apo-carotenoid crocin on acrolein level in AD, another study was carried out and results obtained showed that the levels of p-Tau protein, MDA and Aβ were significantly decreased. Crocin also modulated signaling pathways of MAPKs [83]. As discussed earlier, the BBB play significant role in pathogenesis of AD and drug delivery for treatment of this diseases. The modulatory effect of Crocin on BBB was reported in an in vitro study carried out using bEND3 cell lines treated with Crocus sativus extract which is known to be rich in crocin, the results from this study showed that crocin treatment increased the tightness of cell-based BBB and help to reduced cell Aβ load [84].Transgenic model and C57BL/6 mice were used to examine the efficacy of Crocus sativusin AD. Results obtained showed that daily treatment of animal with diet fortified with 10 mg/kg of crocin for 5months enhanced Aβ clearance pathways via ApoE and BBB clearanceas well as enzymatic degradation pathways in wild type up-regulation of the synaptic proteins and reduction in neuroinflammation process [84]. All these findings indicated that crocin supplement protective role on pathological manifestation of Aβ proteins and cognitive deficit in AD.

3.3. Fucoxanthin

This is another sub-class of carotenoids having epoxy group attached to the carotenoid group. It has a molecular formula of C42H58O6 and exists in marine plants like edible brown seaweeds. This carotenoid had been reported via in silico, in vitro, and in vivo studies to exhibit some brain health beneficial effects such free radicals and ROS scavenging potential, countering inflammatory and amyloidogenic processes implicated in the development of AD [85,86]. For example, report from an in silico study has revealed that this carotenoid inhibits the activity of the amyloidogenic enzyme BACE1 and this type of enzymatic inhibition is a mixed-type inhibition against BACE1, thus fucoxanthin is a potential BACE1 inhibitor. This study was conducted using fucoxanthin extracted from two marine plants namely Undariapinnatifida and Ecklonia stolonifera. Further study conducted via molecular docking revealed that the stimulation of the Glycine and Alanine residue at positioned 11 and 127 in the BACE 1 caused interaction of the two hydroxyl groups in fucoxanthin using negative binding energy of about -7.0 kcal/mol which causes stabilization of the open structural form of the enzyme [87]. Report from in vitroexperiment by pretreatment of SH-SY5Y cells with 0.3–3 μMfucoxanthin and that of molecular docking studies had also revealed fucoxanthin interact with Aβ peptides in a hydrophobic manner, which prevent the conformational changes which lead to self-assembly of Aβ and intracellular ROS generation and as well significantly inhibits the activation of P13K/AKT pathway and inhibition of ERK cascade which prompt Aβ oligomer-induced neuronal apoptosis in SH-SY5Y cells. This report showed that the fucoxanthin effect is in a dose-dependent manner. Thereby prevent the conformational transition and Aβ self-assembly into fibril process leading to decreased neurotoxicity of Aβ oligomers in AD [88,89]. Furthermore, the impact of fucoxanthin on the neurotransmitter esterase enzyme (i.e. acetylcholinesterase) activity and brain-derived neurotrophic factor (BNDF) level have been studied using scopolamine in modeling AD in animal, followed by treatment with of 100 mg/kg and 200mg/kg of fucoxanthinintragastrically. Results from this study showed that fucoxanthin significantly inhibited the activity of acetylcholinesterase (AChE) activity and enhanced the expression of BDNF [90]. Similar results were obtained in another research conducted using Aβ oligomer-induced AD model treated with varying concentration of fucoxanthin for about 16 days resulting in a significant in choline acetyltransferase activity, increased expression of BDNF and reduced level of oxidative stress in the hippocampus of mice [90]. These findings show that fucoxanthin exhibit neuroprotective properties as it attenuates the cognitive impairments expressed in the experimental animal. Nevertheless, one hurdles in efficient use of carotenoid fucoxanthin is that first pass effect which results in low bioavailability with the CNS. The identification of this hurdles, scaling and redesigning of fucoxanthin in nanoparticle form had been suggested and conducted as well [91]. Artificially synthesized polylactic-co-glycolic-acid-bock-polyetheneglycol-loaded fucoxanthin (PLGA−PEG-Fuc) nanoparticles with diameter of about 200 nm was designed and used in an in-vivo study done using Aβ oligomer-induced neurotoxicity. Report from this work showed that intravenous administration of the nanoparticles ehibited much efficacy than ordinary form as this helped to prevent cognitive impairments. This enhanced efficacy was attributed to activation nuclear factor erythroid-2- related factor (Nrf2) and nuclear factor-κB (NF-κB) signaling pathways. These findings indicated that PLGA−PEG-FUC nanoparticles could enhance the bioavailability of fucoxanthin in the hippocampus of AD animal model and serve as potential preventive agent to restore the cognitive impairment in AD [92].

3.4. β-Cryptoxanthin

β-Cryptoxanthin is known to a carotenoid and major vitamin A precursor in fruit like orange, tangerines, mandarins, red pepper, zucchini etc. It has molecular mas of C40H56O. This carotenoid exists in nature and structurally contained hydro-aromatic structure having hydroxyl group as ionizable group its rings [93]. Available evidenceshowed that the level of β-Cryptoxanthin is very low in AD patients when compared with control individual [93,94]. The intake of the plant or products of this carotenoid had been reported exhibit neuroprotective effects as it exhibits anti-oxidative and anti- inflammatory potentials, thus could help in lowering the risk associated with AD pathological.

3.5. Macular Pigments

Macular pigments are dietary carotenoids and pigment. These carotenoids were present in the central retina region called macula. These carotenoids are Lutein, Zeaxanthin, and Mesozeaxanthin. Lutein is an oxygenated carotenoid with a molecular formula of C40H56O2, it is a yellow-colored pigment carotenoid and present in green leave vegetables such as spinach and pepper (black), and structurally it possessed an alpha conformation with hydroxyl-aromatic group than oxygenated carotenoid [95]. The low level of Lutein had been linked with the pathogenesis of AD. Lutein show neuroprotective effect against cognitive decline and the risk of AD in human due to its free radicals and ROS scavenging action coupled with anti-inflammatory actions. The presence of hydroxyl group in the structure of Lutein accounted for its free neuroprotective activities as it enables it to span through and as well concentrate within the brain at higher concentration [96, 97]. Zeaxanthin is another Macular pigments of which shared the same chemical formula with Lutein. Although both are not stereoisomers. Structurally, Zeaxanthin is made up of 40 carbons long molecule intra-span with 11 conjugated double bonds. The carotenoid is responsible for the color pigment in saffron plants, and its stereoisomer Meso-zeaxanthin has been obtained in large quantity in marigolds petal [98, 99]. This zeaxanthin also exhibit similar health beneficial effects with lutein, in that it showed antioxidative and neuroprotective potentials and this had been experimentally proven to help in improving cognitive function deficit associated with AD pathogenesis [100,101]. Aside this, research report on AD had shown that there is retinoic acid (RA) signaling impairment in AD, which additionally accounted for mitochondrial function impairment, oxidative stress, neuronal inflammation and neuronal degeneration pathology in AD. Zeaxanthin in an in vitro study performed by treatment of RA-treated human SH-SY5Y cell lines with 5 μM for 24 hrs, had proven to exhibits neuroprotective effects against GSK-3β hyperactivity associated with tau phosphorylated kinase over-expression, endoplasmic reticulum stress, oxidative injury and phosphorylation of Tau (Ser 396 and Thr 231), implicated to impaired with the normal cellular activity in AD patients [100]. This report affirmed the earlier report made in U.S. Third Nutrition and Health Examination Survey (NHANES II), that the serum levels of macular pigments (Zeaxanthin, and Lutein) and lycopene are associated with risks of AD development in humans. This report was made after assessment of 6958 AD patients above 50 years old and result indicated that higher serum levels of carotenoids: zeaxanthin, lutein and lycopene would help in lowering the risks of developing AD [101]. In addition, report from another human intervention studies done as a randomized and double blinded clinical trial with placebo using 31 AD patients and 31 age-matched control as subjects to elucidate the synergistic effects of the macular pigments supplements administered as macushield (containing 10 mg of lutein, 2mg of zeaxanthin and 10mg of mesoxanthin) or as placebo using sunflower oil for 6 months, had shown that the supplements exhibit synergistic effect as it significantly improved serum level of macular pigment in both AD and non-AD group which accounted for the improved vision and cognitive function in AD patient[102,103]. Therefore, the intake of macular pigment would help to improved cognitive function in AD.

3.6. β-Carotene

Among the subclass of carotenoids is carotenes, these are carotenoids without oxygen. They are further subdivided into α, β, γ, δ-carotenes and lycopene, but attention would be centered on the two most common carotenes, namely β-carotenes and lycopene due to their neuroprotective actions in suppressing AD symptoms. β-Caroteneis known to be responsible for red-orange pigment in plants. It occurs naturally as retinol, which is known to be a vitamin A precursor. It has a molecular formula of C40H56. The hydrocarbon chain in this carotenoid enables it to act as a free radical scavenger, thus acting as an antioxidant. Biomedical research has revealed that its supplement in food exhibits free radical scavenging and protects against amyloid fibrils protein formation in AD using animal models. In AD research, the use of streptozotocin (STZ) in modeling Sporadic AD has already been established since the administration of STZ via Intracerebroventricular (ICV) in experimental animals is associated with cognitive impairment [104]. A report from in vivo study showed that the administration of β-carotene supplements significantly improved cognitive function in STZ-induced AD in mouse. As reported during this in vivo study two doses (1.02 and 2.05 mg/kg) of β-carotene were administered for fourteen days consecutively after induction of AD in the animals. Results obtained showed that both doses reduced STZ-induced cognitive deficit and the efficacy was in a dose-dependent manner as those treated with 2.05 mg/kg β-carotene appreciable improvement inexpressing their cognitive functions [105]. Acetylcholine (ACh) is an important neurotransmitter thatplaysa crucial role in signal transduction of neural and mental health. This neurotransmitter has been implicated in the pathogenesis of AD [105]. Neurological research reportshave shown that treatment of AD model animal with 2.05 mg/kg b.wgt of β-carotene significantly helped to ameliorate the pathological features in the AD by reducing the activities of the cholinergic enzyme acetylcholinesterase, which hydrolysesacetylcholine to acetic acid and choline in postsynaptic nerve, thus reducing the Aβ protein formation and fragmentation in AD, since the β-carotene possessed free radical scavenging which promotes amyloid fibrils formation implicated in the pathogenesis of AD [105,106]. In another report showing an interlink between the level of β-carotene and AD pathogenesis, the level of β-caroteneis found to be generally low when compared with healthy individuals, thus depicting the involvement of plasma or serum concentration of β-carotene in the pathogenesis of AD [107,108]. Likewise, in a cohort study of 31 age-matched healthy individuals and 37 patients of AD with respect to interlink betweenβ-caroteneand accelerated cellular aging markers likes leucocyte telomere length and peripheral blood mononuclear cells (PBMC) telomerase activity, significant reduction in β-carotene level was reported in AD patient as compared to healthy control was reported. This report is in accordance with the lower plasma level of β-carotene level observed during in diagnosis of AD [109]. In addition, synergistic interaction with other antioxidants was also reported for β-carotene in AD study. B-carotene can act synergistically with other antioxidantslike vitamin C and E, thus forming vitamin complexes as observed in an in vitro study performed by incubating with PBMC of an AD patient when compared with the healthy control. This vitamin complexwas reported to be potent in reducing the free radicals, ROS, and pro-inflammatory cytokines generations, thus reducing oxidative stress with the PBMC and inflammation in AD patients thereby increasing the antioxidant and anti-inflammatory capacities of the cells [110].

3.7. Xanthophylls

Xanthophylls are yellow pigment carotenoids andare also referred to as phylloxanthins. There are diverse forms of phylloxanthins in nature because they exist in different forms, which include glycosides, protein complexes, sulfates, and fatty acids. At present, there are more than 700 kinds of xanthophyll that have been identified including β-cryptoxanthin, zeaxanthin, astaxanthin, fucoxanthin, and lutein. The available research evidence has pointed out the role of some xanthophyll in the management of AD. Among these xanthophylls is Astaxanthin, a xanthophyll thatexists as a structural carotenoid component of some aquatic organisms such as yeast, complex plant, fungi, red-colored aquatic organisms, seafood, plankton, and microalgae [111]. Structurally, it is a keto-carotenoid, thus it is placed under xanthophylls due to the fact that it has oxygen-containing components in its ring structure. [112,113]. The neuroprotective and anti-Alzheimer activities had been attributed to its strong anti-oxidative, anti-inflammatory, lipid peroxide formation-preventing effects. The presence of two hydroxyl substituents at positions 3 and 3′ in its structure enable it to scavenge ROS and can also enable it to donate electron in reaction thereby preventing lipid structure attack on the interior and exterior part of the cell membrane [114]. Evidence of these were also reported in both in vivo and in vitro studies [115,116]. Compromised integrity of the blood-brain barrier of the endothelial cells at the tight junction leading to disruption of the tight junctions is another pathological feature of AD. Although the accumulated amyloid protein (i.e αβ peptides) is responsible for this compromise in the integrity of BBB at the tight junction since the accumulated amyloid protein caused blockage of transport of proteins leading to alteration in the expression, synthesis, and transport of structural tight junction proteins. These pathological effects caused the activation of the inflammatory process and brain hypo-perfusion expressed in AD [117]. To mitigate these effects, the combined effect of astaxanthin and bexarotene (Asx/Bex) on amyloid precursor proteins (APP) has been studied. The bexarotene is known to be a retinoid x receptor agonist. The combined effect of Asx/Bex exhibited synergistic effects on suppressing the processing andproduction of APP and αβ peptides, as well as their transfer within BBB of triple transgenic AD (3×Tg AD) mice and through the primary porcine brain capillary endothelial cells (pBCEC)[115]. Results obtained showed that this complex treatment caused down-regulation of the amyloidogenic BACE1 transcriptional processes, and reduced the level of Aβ oligomers, while it enhanced the soluble α-APP production and non-amyloidogenic and metalloproteinase domain containing protein 10 (ADAM10) (an enzyme α-secretase that facilitate its catalytic cleavage of the APP in non-amyloidogenic pathway and as well inhibiting the formation of Aβ peptide. Furthermore, the synergistic effect also promotes clearance of Aβ to the apical [115]. In another study carried out using AD Mouse model, similar results were observed upon administration of 80 and 100 mg/kg of Asx/Bex complex respectively for six days to 3×Tg AD. Reduction in the expression of BACE1 with elevated level of expressed low-density lipoprotein receptor-related protein 1 (LRP-1) in pBCEC of AD transgenic mice [115]. Furthermore, increased in IRS-S307 (Insulin Receptor Substrate-1) and glycogen synthase kinase-3 (GSK-3β) activities were another experimental finding reported as pathological features in hippocampus of brain of AD, the increased in IRS is due to phosphorylation of IRS-1 at serine residue positioned 307 [116]. Although the receptor plays a resistance role in the central and neuronal cells to insulin, its phosphorylation increases insulin resistance [116,117]. Likewise, phosphorylation of GSK-3β enhanced its overexpression which have been implicated in AD. The role of astaxanthin in mitigating the pathological changes had been reported in a study [118]. As reported, orally administration of astaxanthin at doses of 0.5mg/kg and 1 mg/kg for 28 days significantly reduced IRS-S307 and GSK-3β activities and as well reduced the level of soluble Aβ1–42, thus, attenuating the cognitive and memory impairment associated with AD as revealed via cognitive and brain test assessment like Morris Water Maze and Novel Object Recognition tests [119]. In this same study, the level of the neurotransmitter (AChE), inflammatory cytokines (TNF-α), lipid peroxidation, and nitrosative stress in the brain were significantly reduced in the hippocampus of treated group. To affirmed this, histopathological report of the hippocampus of brain of AD rats also structurally confirmed anti-amyloid protein formation prevention and neuroprotective effect of astaxanthin [119]. In addition, antioxidative and anti-inflammatory effects of its diesters have also been reported. The study was conducted by the administration of docosahexaenoic-acid-acylated-acylated astaxanthin, which is astaxanthin diesters (AST-DHA) in to a double transgenic AD mouse model which expresses APP/PSEN1 genes for 2months. Result obtained shows enhanced memory, cognitive skills and learning of APP/PS1 mice through reduction of hyper-phosphorylation of tau protein, oxidative imbalance and neuronal inflammatory biomarkers [120].

3.8. Lycopene

This is another type of organicpigment thatcontributes to the red pigment of fruits and vegetables. It is a light red acyclic carotenoid, it exists naturally in some plant like tomatoes, sweet red peppers, guava, and watermelon [121]. Several reportshave shown the anti-oxidative potential of this phytochemical, most especially on cellular macromolecules. In AD, lycopene has been reported to help in reducing lipid peroxidation and DNA damage as reflected by the low level of expression of their lipid peroxidation and DNA damage biomarkers, thus exhibiting neuroprotective potentials against AD pathogenesis [122,123]. Much workhave been done via in vitro and in vivo studies using its supplement to establish its role in suppressing or ameliorating the AD pathological features. Report from biomedical research using M146L (double-transfected human APP gene and presenilin-1gene) cells, which overexpressed Aβ made by double-transfection with human APP gene and presenilin-1 gene in Chinese hamster ovary cells. Treatment was done using 10 μM of lycopene for 24hrs [124] and the result showed that the lycopene inhibits enzymatic activities of amyloidogenic β-secretase (BACE1) (enzyme which promotes amyloid proteins synthesis) activities; alleviates pathological process of oxidative stress and apoptosis, down-regulates the pro-apoptotic proteins, up-regulates the anti-apoptotic proteins and antioxidants levels and as well enhancing induction and activation of Nrf2/ Akt/ P13K signaling pathways [124]. Report from neuroprotective research conducted by administration of 2.5 mg/kg and 5 mg/kg of lycopene into Aβ1−42 treated AD rat for 3 weeks showed that lycopene reduced the effect of mitochondrial oxidative damage and neuroinflammatory process, restored the level of brain-derived neurotrophic factor (BDNF) and as well improved memory in rat [125]. These results were similar to the report presented by treatment of lipopolysaccharide (LPS)-induced AD rat with Lycopene at a dose of 15 mg/kg body weight for a month, as a significant decrease in the production of inflammatory cytokines andoxidative stress with a reduction in pathological lesions in the hippocampus of AD rats were observed [126]. In addition, a report from another neuroprotective effect study of lycopene showed that administration of 0.2-0.5 μM lycopene for about 24hours resulted in inhibition of the apoptotic process stimulated by Aβ via some mechanisms which include inhibition of mitochondrial dysfunction, suppression of NF-κBexpression in neuronal SHSY5Y cells andreduction of ROS production [127]. These results reflect the efficacy of lycopene in combating and suppressing AD pathological features.

4. Future Prospects

Lately, a lot of scientific developments have changed how carotenoid supplements are used to treatAD. The development of nano-formulations containing carotenoids to increase their bioavailability and blood-brain barrier crossing efficiency has been made possible by bionanotechnology systems. This presents a strong opportunity to enhance their therapeutic impact on cognitive function [128-131]. The field of synthetic biology has further facilitated the conversion of carotenoids into refined compounds, resulting in carotenoid molecules possessing enhanced properties including increased potency, stability, or specific targeting of brain cells affected by AD [132-136]. Optimized absorption was made possible by the application of gene editing techniques to change the genes directing carotenoidsynthesis, including microbial production, inrelation to the human body's requirement and metabolism [137-140]. The enhanced supplements increase the body's ability to absorb and use these compounds, increasing their potential to ameliorate cognitive deterioration [141-144]. Examining the connection between carotenoids and the stomach microbiota has become more feasible based on manipulation of the microbiome. Supplements containing carotenoids are, therefore, made to support a healthy gut environment, leveraging the brain-gut axis as a dependable link between gut health and brain function [144-147]. Avatars may also be built in medicine to identify biomarkers for individualized care, particularly in communities of color as a result of gene–environment interactions in the disease expression [147-149]. It may be more effective to use bionanotechnology to identify biomarkers that indicate an individual's susceptibility to the hitherto incurable and highly debilitating AD or their response to taking carotenoid supplements. Oligopeptide as well as PS-80–coated PBCA dextran polymeric nanoparticles have been employed as activatablefluorescent probes and targetable vehicle probes across the blood-brain-barrier to facilitate the visualization of Aβ plaques in Alzheimer's disease model. Using this data to develop customized treatment plans will guarantee more accurate outcomes [150,151]. Personalized recommendations for carotenoid supplements can be produced using precision medicine and AI integration. AI-driven algorithms are used to assess genetic, lifestyle, and health information, including family history. This approach allows for the optimization of dosage and composition to match each individual's specific demands [152-157]. Formulations of carotenoids with neuroprotective qualities in addition to symptom alleviation could be improved by researching and modeling the neuroprotective processes of carotenoid supplements for individuals through several potential routes of administration [158-162]. These might include hydrosol, a type of biomaterial-enhanced formulation, which is administered via the intranasal (nose-to-brain) route [163-165]. These formulations offer optimism that the progression of AD may be prevented or slowed down. The field of carotenoid supplements can build upon these scientific advancements to control and potentially even prevent AD, rather than just treating its symptoms. If these findings are taken into consideration, treatment and care for these conditions may change significantly.

5. Conclusion

Alzheimer's disease is aprevalent neurodegenerative condition impacting millions worldwide, marked by progressive cognitive decline and memory impairment. Despite lacking definitive cures, emerging evidence underscores the potential influence of specific dietary components, notably carotenoids, in both prevention and management. Carotenoids, natural pigments abundant in various fruits, vegetables, and algae, not only lend vibrant hues to plants but also crucially contribute to photosynthesis. Beyond their role as colorants, carotenoids exhibit robust antioxidant and anti-inflammatory characteristics, demonstrating diverse health advantages, including shielding against neurodegeneration. The neuroprotective effects of carotenoidsstem from multiple mechanisms. Carotenoids adeptly neutralize free radicals, highly reactive molecules capable of cell and DNA damage. This antioxidative prowess shields neurons from oxidative stress, a pivotal factor in neurodegeneration. Also, Carotenoids regulate inflammatory signaling pathways, diminishing the production of inflammatory agents that fuel neuroinflammation, a significant contributor to neurodegenerative disease progression. Carotenoids modulate cellular signaling by interacting with diverse cellular signaling pathways, influencing cell survival, apoptosis, and gene expression. These interactions potentially bolster neuroprotection by enhancing neuronal resilience and optimizing cognitive function. Extensive preclinical investigations have highlighted the neuroprotective capacities of carotenoids within animal models exhibiting Alzheimer's disease (AD) pathology. These studies underscore the ability of carotenoids to mitigate the aggregation of amyloid plaques and neurofibrillary tangles, pivotal pathological hallmarks of AD. Moreover, they demonstrate enhancements in cognitive performance and a delay in the onset of neurodegenerative processes. Human clinical trials further substantiate these findings, indicating the neuroprotective potential of carotenoids. Epidemiological evidence suggests a correlation between heightened dietary intake or elevated blood levels of specific carotenoids—such as lutein and zeaxanthin and reduced susceptibility to dementia or AD. Furthermore, select intervention studies indicate that supplementation with carotenoids may ameliorate cognitive functions in individuals with mild cognitive impairment or in the early stages of AD. Taken together, carotenoids, with their potent antioxidant and anti-inflammatory properties, have emerged as promising candidates for neuroprotection in AD. While more research is needed to fully establish the mechanisms of action, their efficacy, safety, the optimal dosage and duration of carotenoid supplementation for neuroprotection, the available evidence suggests that dietary intake or supplementation of certain carotenoids may offer a beneficial strategy for preventing and slowing the progression of these devastating neurodegenerative disorders. Also, future research should focus on identifying the most effective carotenoids and combinations of carotenoids for neuroprotection, as well as determining the optimal timing and dosage for supplementation.

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