Chapter 10
Role of Antioxidants, and Lifestyle in Managing Brain Disorders Oxidative Stress Biomarkers and Antioxidant Treatments in Brain Diseases

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10.1 Introduction

Alzheimer's Disease (AD), schizophrenia, and Autism Spectrum Disorder (ASD) are brain diseases that are the most current and popular research topics today. These three diseases occur in different periods of the life cycle. Investigation of the pathophysiological conditions of the brain continues with the emergence of these diseases especially in infancy, schizophrenia in youth, and AD in later ages. In addition, these three diseases fall into three different definitions in the field of brain diseases: neurodevelopmental disorders, neuropsychiatric diseases, and neurodegenerative disorders.

Oxidative stress can cause neurodegeneration by creating neurotrauma, especially when it occurs in neuron cells. For example, excessive reactive oxygen (ROS) and nitrogen (RNS) species, activity may impair neuronal signal transmission by myelin sheath damage by causing an imbalance of Ca^{2+} in the neuron cytoplasm [1]. Antioxidants are an innate class that regulates free or ROS depending on the damage caused by oxidative stress. While ROS belonging to our cells are produced by ETS in mitochondria, many enzymes, including superoxide dismutase (SOD) and

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glutathione peroxidase (GPx), which provide defense in times of stress and damage, act as ROS cleaning agents [2]. The brain is under more effective hyperbaric pressure than any other tissue in our body. This suggests the need for oxygen to produce adenosine triphosphate (ATP), which is required to continue oxidative phosphorylation in neural mitochondria and control vital mechanisms. The most of oxygen amount (almost %90) is utilized in oxidative phosphorylation in mitochondria and observed in the form of electron reactions in the electron transport chain (ETC). In some cases, however, oxiradicals from oxidation of molecules can leak into the cytoplasm, with electrons avoiding ETC, and may cause many types of peroxidative reactions that disrupt mitochondrial matrices and lipid membranes [3]. So, oxidative stress may play a crucial role in the pathophysiology of certain neuropsychiatric diseases, including AD, schizophrenia, and autism. Identification of readily accessible biomarkers is obligatory to let better diagnosis and control of brain disorders because much more effective therapies can be developed by looking at the effects of both drugs and many other alternative treatments with both cognitive and biomarkers levels. In this book chapter, we provided a deep insight into the main players in the neural mechanisms of antioxidants and particularly touched upon their effects on AD, schizophrenia, and autism, which cannot remove from the world of secrets. We tried to discuss updated and limiting aspects of oxidative stress biomarkers and the therapeutic effects of antioxidants on their potential in neuronal activities.

10.2 Schizophrenia

10.2.1 Oxidative Stress Biomarkers

The neuropathophysiology of schizophrenia was tried to be explained depending on the activity of dopamine pathways in the brain; In particular, the high activity of positive symptoms of the disease due to dopamine in the mesolimbic pathway and low activity in the frontotemporal region cause negative symptoms [4]. The diagnosis of schizophrenia is based on the clinician's subjective interpretations of the negative and positive symptoms of the disease. Investigation of molecular biomarkers of this condition has a very important place in the limited evaluation of clinical symptoms in many psychotic diseases, including schizophrenia [5]. The effects of neuronal oxidative stress in the pathophysiological studies of schizophrenia have begun to be clarified. In a systematic review of metabolite biomarkers of schizophrenia patients, elevated lipid peroxidation metabolites, glutamate, and decreased essential polyunsaturated fatty acids (EPUFAs), vitamin E, and creatinine levels were detected in blood serum samples [6]. In another systematic review and meta-analysis, TAS and docosahexaenoic acid levels were significantly lower, and in contrast, homocysteine, interleukin-6, and tumor necrosis factor-alpha levels were significantly higher in 3002 first-episode or early schizophrenia patients compared to 2806 control group [7].

Antioxidant enzymes have many complex and unclear functions in human nature, including SOD, GpX, and catalase (CAT). These enzymes suppress the initiation of many damaging chain reactions of reactive species [8]. Interestingly, Buosi et al. (2021) found lower SOD levels, higher malondialdehyde (MDA) and CAT levels, and the same GPx, total glutathione (GSH-t), and Trolox-equivalent antioxidant capacity (TEAC) levels in treatment-responsive and treatment-resistant schizophrenia patients compared to healthy group [9]. Cruz et al. (2021) found poor performance in working memory tests associated with higher serum levels of thiobarbituric acid reactive substances (TBARS) in 85 stable schizophrenia patients compared to a control group (n=75) [10].

Kim et al. (2019) measured the strong oxidant iridium (Ir) to examine the oxidative damage serum samples of 73 schizophrenia patients and 45 healthy people and found no significant differences. Likewise, the schizophrenia group treated with clozapine showed higher levels of oxidative stress and it was concluded that clozapine may cause this damage [11]. Another interesting finding was that oxidative stress levels in the serum could be related to oxidative stress in the cerebrospinal fluid (CSF), which may facilitate the diagnosis of schizophrenia in the future because neuroinflammatory and oxidative stress markers can cross the blood-brain barrier (BBB) [11, 12] GPx levels were low in the drug-free group, but total antioxidant capacity (T-AOC) and SOD levels were not significant in both groups in a total of 80 patients with schizophrenia (40 non-drug, and 40 medication use patients). In addition, GSH-Px and MDA were upregulated in the medication group, but SOD levels were reduced in patients Bai et al. (2018) and Juchnowicz et al. (2021) reported that GSH, total oxidant status (TOS) and GPx values are the most promising in the differential diagnosis of schizophrenia [13, 14]. On the other hand, the differential diagnosis of serum kynurenine (KYN) (lower in serum), enhanced oxidation protein products (AOPP), TAC, and nitric oxide (NO) levels among patients with chronic schizophrenia with the early diagnosis was ultimately promising. Importantly, KYN and TAC could be a biomarker for the treatment response. Also, other significant differences were found in terms of T-AOC, glutathione reductase (GR), total protein, enhanced glycation end products, the ferric reducing ability of plasma (FRAP), SOD, TOS, dityrosine, N-formylkynin urea levels [14]. In addition, the investigation of oxidative biomarkers in healthy and schizophrenia groups may provide an additional evaluation criterion for schizophrenia patients to diagnose and respond to treatment in the future. In a clinical study, the concentrations of monocyte chemotactic protein-1 and interleukin-8 were significantly higher and there was no significant difference in the serum concentrations of heme oxygenase-1 and 8-Hydroxydeoxyguanine in patients with schizophrenia compared to the control group [15]. For another oxidative stress marker study, oxidative stress index (OSI), TOS, myeloperoxidase (MPO) and Disulphide (DS) parameters were significantly higher and total antioxidant status (TAS), total thiol (TT), native thiol (NT) levels were significantly lower in Schizophrenia groups [16]. Grignon and Chianetta (2007) determined oxidative stress among patients with schizophrenia and reported a very high increase in MDA levels [17]. Zhang et al. (2010) reported upregulated NO and TBARS levels in schizophrenia patients' serum [18].

Oxidative stress also has many effects on DNA, because DNA has many negatively charged phosphate groups, it can bind many different cations such as $Fe^{+2/+3}$ and $Cu^{+1/+2}$, and these ions can be catalyzed by H_2O_2 if they bind to negatively charged DNA under oxidative stress [19]. For such a reason and beyond, bases and nucleic acid sugars may be modified due to oxidative stress, and damage due to single/double chain breaks may occur with the rupture of hydrogen and even covalent bonds[20]. Copoglu et al. (2015) found TAS, OSI, and 8-hydroxydeoxyguanosine (8-OhdG) serum levels were significantly elevated in without symptomatic group, TOS and OSI levels were significantly higher and TAS levels were significantly lower in the symptomatic schizophrenic patients, DNA damage was higher in only without symptomatic group compared to controls [21]. Animal studies have shown that some brain areas are affected differently by oxidative stress than others, and 8-OHdG levels were changed in different brain regions. A negative correlation was found between DNA damage in the detected regions and the effort of DNA to destroy 8-OhdG [22]. In a postmortem study, the 8-OHdG level was quite higher in the hippocampus of schizophrenia [23]. There may be situations where cells cannot cope with oxidative stress [24], in such cases, DNA cannot be repaired and cell death (apoptosis) occurs, especially in brain diseases [25]. This manifestation of apoptotic processes has been associated with many neuropsychiatric diseases, including schizophrenia, and has been associated with tumor suppressor elements. The study emphasized that about p53 for the regulation of apoptosis and explored the potential and sensitivity of nucleic acid in schizophrenia [26]. Damage in DNA or dysfunction of repair mechanisms may be a factor triggering apoptotic pathways [27] due to impaired intracellular signaling of hyperphosphorylated p53. Proving these theories, Levine (1997) reported that p53 is not active in healthy cell activity, but can be activated in DNA damage [28].

Level inconsistencies can be seen in many biomarkers attributable to oxidative stress. These may be caused by differences in the measurement techniques of these levels, differences in the tested material, medication, and different phases of the disease. Family history of the disease, geography, lifestyle, physical activity, and nutritional status may be the source of such problems.

10.2.2 Antioxidative Treatments

Drug therapy in the treatment of this disease is limited to antipsychotics. Although many drugs used in the clinic are important for the treatment of schizophrenia, they have not been satisfactory in managing the disease completely. Therefore, alternative treatment options are urgently needed. One possible way could be antioxidant therapy. For this reason, elucidating the antioxidant mechanism may suggest future treatment options and thus be more successful in the management of schizophrenia.

Also, findings regarding antioxidant enzyme levels in the earliest periods of the psychotic disorder may be contingent on the type of drug, the harshness of the psycho-pathology, or environmental circumstances. For example, studies are showing decreased GSH concentration in the CSF, prefrontal cortex, and postmortem caudate of schizophrenic patients [29–31]. Interestingly, most of the studies on antioxidant defense in patients reported a decrease in the defense system [8, 32–37], there are also studies in the literature that argue the opposite [38–41].

The most commonly used antioxidants in studies conducted with schizophrenia patients were vitamins C and E. As well known, Vitamin E is a fat-soluble vitamin that can keep from radicals that cause oxidative stress. However, cytosolic proteins, from which most harmful radicals are produced, have little potential to prevent oxidative damage to mitochondria and nuclei. Therefore, it makes sense to put together a water-soluble vitamin C along with the treatment [41].

Increasing research on the therapeutic potential effect of second-generation antipsychotics in the treatment of schizophrenia continues rapidly. Microglial cells in the brain show a protective effect against the production of ROS and RNS, which cause neuroinflammation against oxidative stress. ROS and RNS production cause neurodegeneration, white/grey matter abnormity, and decreased neurogenetic actions observed in schizophrenia [42] (in Fig. 10.1). Several studies have

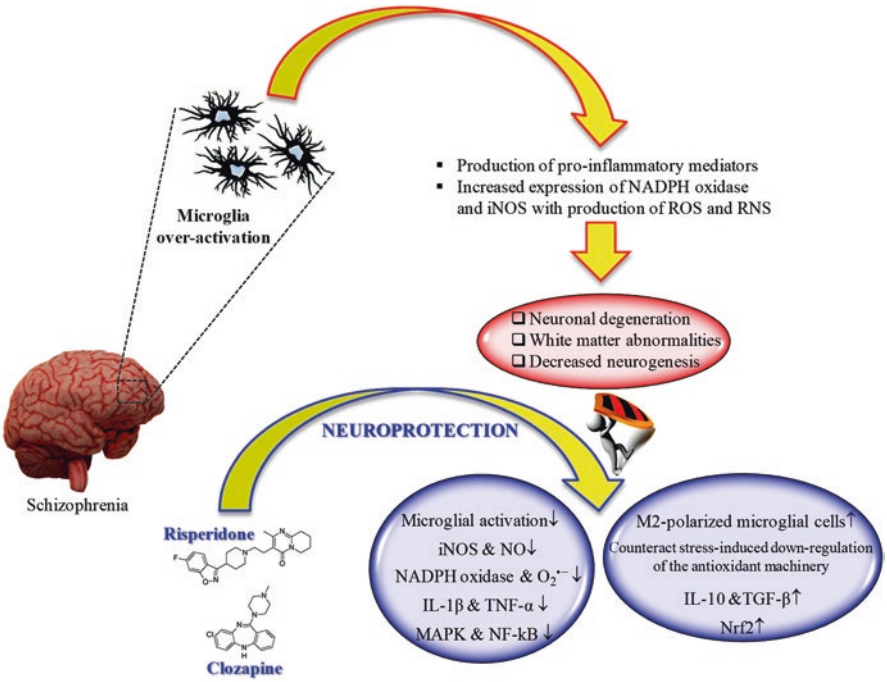

Fig. 10.1 Schematic representation of the oxidative effect of common second-generation antipsychotics used in schizophrenia on microglial cell activations, ↑ = increased; ↓ = decreased [50]

demonstrated the antioxidant and anti-inflammatory of second-generation antipsychotics on the regulation of microglia activity, specifically for proinflammatory cytokines, ROS and RNS. The experimental animal study reported that paliperidone (1 mg/kg i.p.) has the potential option to treat antioxidant and anti-inflammatory pathways in acute and chronic rat stress modeling [31]. Interestingly, Eneni et al. (2020) investigated the effects of haloperidol (1 mg/kg, i.p.), Disomine (25, 50, and 100 mg/kg, i.p.), and risperidone (0.5 mg/kg, i.p.) on schizophrenia-like behavior and the fundamental changes in oxidative stress biomarkers and acetylcholinesterase (AChE) activity in mice. While Disomine and Risperidone ameliorated acute and subacute ketamine-induced schizophrenia-like behaviors, cognitive status was better in the disomine-treated group, with high SOD and GSH levels and low levels of MDA and AChE [43].

As reported in the 12-week prospective longitudinal study results, the patients presented higher SOD, CAT activities, and TAS levels, but lower MDA levels and GPx activity after receiving risperidone monotherapy. The authors showed that the antioxidant defense enzymes and redox regulatory system may contribute to these values as a response to risperidone therapy in patients with schizophrenia [44]. In Yolland et al. (2020)'s study, a meta-analysis of randomized controlled experiments, total scores and cognitive status with working memory was significantly improved in the N-acetylcysteine group after 24 weeks of treatment [45]. Ermakov et al. (2021) suggested that not only antioxidants but also drugs targeting the redox-regulated transcription factor (including Nrf2 and FoxO activators or NF-kB inhibitors) have a distinguished promise in schizophrenia [46]. In an animal study, aripiprazole, ziprasidone, and olanzapine regulated ROS levels, SOD activity, and BCL2-related X protein (Bax) expression in mouse pheochromocytoma (PC12) cells to be protective against oxidative stress caused by 1-Methyl-4-*phenylpyridinium* (MPP+) ion [47, 48] In the ketamine-induced model, a permanent decrease was detected in the GSH/GSH disulfide ratio and parvalbumin expression in the medial prefrontal cortex. In addition, it caused a decrease in mitochondrial membrane potential while also increasing superoxide levels. In the synaptic examination, the excitatory and inhibitory effects were disrupted in the pyramidal cells, but the mitochondrial function returned to normal in the pyramidal cells with the applied NAC [49]. More studies on antioxidant treatments in schizophrenia are needed.

As Minarini et al. (2017), and Miyake and Miyamoto's (2016) papers showed that in randomized controlled trials, treatments with N-acetylcysteine (NAC), a powerful antioxidant added to antipsychotics, are effective in patients with chronic schizophrenia [51, 52]. The results of using a neurodevelopmental model of schizophrenia and also in clinical studies suggested that NAC may have promising effects in an early stage of schizophrenia and an at-risk mental state [51–54].

10.3 Autism

10.3.1 Oxidative Stress Biomarkers

ASD is defined as a neurodevelopmental disorder with a prevalence of at least 1%. Based on ASD, there are a series of brain studies that try to explain multigenetic, and epigenetic factors with environmental factors and the systems such as serotonergic and glutaminergic [55]. The symptoms of the disease include cognitive and social deficits as well as sensory disorders that begin in the developmental period of childhood [56]. Due to the multifactorial etiology of ASD, both the understanding of the mechanism of the disease and its treatment are complex. Haile et al. (2017) pointed out several mechanisms that may develop mitochondrial dysfunction due to oxidative stress in mitochondria. This situation can lead to misfolding of many proteins associated with mitochondrial membranes in the endoplasmic reticulum (ER) (e.g., guanosine triphosphatase (GTPase) Rab32), which may also be a precursor to many neurological disorders [57]. The cell also has an innate defense mechanism, particularly the expression of CYP cytochrome and many transcriptional factors (e.g., nuclear factor (erythroid-derived 2)-like 2 (Nrf2)) in response to oxidative stress [58].

Numerous studies on the pathogenesis of ASD have reported findings of increased oxidative stress levels which lead to DNA damage, neuroinflammation, weakened immune system and epigenetic impairment, and decreased antioxidant capacity in patients with ASD [59, 60]. In particular, factors such as oxidized biological markers, heavy metals, herbicides, pesticides, and UV light have been suggested for the relationship of ASD-related oxidative damage with environmental factors [61].

Two different studies reported that children with ASD were powerless against increased GSH in their plasma and decreased GSH levels in their neurons, and thus oxidative stress repair due to storage GSH deficiency [62, 63]. GSH, a thiol tripeptide class, is a powerful antioxidant for neurons (ie. effective for scavenging free radicals in dopamine neurons in the substantia nigra pars compacta). As a result, it is a powerful antioxidative agent with a neuroprotective effect by preventing neuroinflammatory reactions related to oxidative stress in ASD, especially Lipid peroxidation in newborns [64, 65]. Likewise, Rose et al. (2016) showed that plasma GSH storage of a child with autism decreased compared to his normally developing sibling, and this discrepancy would occur in cells sensitive to oxidative stress [62]. Interestingly, Burger et al. (2017), in their case study, underlined genetic biomarkers in the metabolic assessment of oxidative stress in children with ASD as a result of whole-exome sequencing (WES), a new c.795delT mutation in the WDR45 gene in a sibling with autism. They reported that this mutation has raised the mitochondrial activity of complex I+III in both muscle and fibroblasts due to elevating the respiration in peripheral blood mononuclear cells (PBMCs) [66]. Rose et al. (2016) associated this situation with stereotypical behaviors due to mitochondrial dysfunction in their study comparing sibling samples of ASD in vitro [62]. Mitochondrial dysfunction in ASD may be because redox inconsistency in this part results in oxidative

stress and may be due to background gastrointestinal system (GIS) dysregulation [67].

Chauhan et al. (2004) concluded that oxidative stress may be higher by reporting that plasma lipid peroxidation and amino-glycerophospholipids level in the ASD group was more increased compared to their normal developing siblings and AGP levels could be a biomarker for ASD[68]. In Efe et al.'s (2021) study, of 60 children with autism, in which dynamic thiol/disulfide homeostasis (DTDH) levels could be a marker of oxidative stress, they reported lower plasma thiol levels in contrast to high disulfide and thiol oxidation-reduction ratio in plasma but showed that these oxidative stress biomarkers were not correlated with autism symptom severity [69]. Needham et al. (2021) examined plasma and stool samples from children with ASD and normal development. Differences were found in amino acid, lipid, and xenobiotic metabolism, oxidative stress, mitochondrial dysfunction, elevated hormone levels, changes in lipid profile, and levels of phenolic microbial metabolites [70].

James et al. (2004) reported that methionine, SAM, homocysteine, cysteine, and GSH-t levels were lower in children with ASD2 compared to healthy controls, while S-adenosylmethionine (SAM), S-adenosylhomocysteine (SAH), adenosine and oxidative glutathione (GSSG) levels were higher in blood plasma [71]. These values can be considered in the class of oxidative stress biomarkers. In a systematic review and meta-analysis of 87 studies (4928 ASD children and 4181 healthy control (HC) children), it was reported that blood nitric oxide, MDA, GSSG, homocysteine, S-adenosylhomocysteine, and copper levels were observed to be higher in children with ASD. However, the blood GSH-t, GSH/GSSG, tGSH/GSSG, GSH, vitamin B9, cysteine, methionine, vitamin B12, vitamin D, vitamin E, SAM/SAH, and calcium concentrations were significantly low in children with ASD [72]. In another systematic review and meta-analyses, although plasma GSH (27%), GPx (18%), methionine (13%), and cysteine (14%) levels were lower and oxidized glutathione (45%) concentrations were higher in ASDs, superoxide dismutase, homocysteine and cystathionine were significantly more no difference detected. The meta-OR of ASD exposure to homozygous mutant subjects (TT) relative to non-homozygous mutant (CC) C677T allele distribution in the methylene tetrahydrofolate reductase gene (MTHFR) was 2.26 [73]. Filippek et al. (2004) found that free carnitine and pyruvate levels were high at low ammonia and alanine levels in 100 ASD children [74], but there was no control group to compare and they only evaluated against reference ranges of values. Impaired ammonia, alanine, carnitine, and pyruvate levels could be an indicator of impaired mitochondrial energy production. Elevated lactate: pyruvate ratio in the cytoplasm of cells may also indicate an impaired cellular redox state resulting from mitochondrial dysfunction. Oliveira et al. (2005) found a higher ratio of lactate and lactate pyruvate in blood plasma in 20% of 69 children with ASD compared to healthy children [75].

Interestingly, in a study of parents of children with autism, the presence of impaired oxidative profiles was a possible factor and highlights the role of genetics in the development of autism [63]. Several oxidative biomarkers were significantly altered in persons with autism, strongly supporting the role of abnormalities in oxidative homeostasis in the pathophysiology of autism. Although valuable findings

were found in all these studies, more comprehensive studies on biomarkers for oxidative stress are needed.

10.3.2 Antioxidative Treatments

Although there is no effective medicine for autism, current pharmacological treatments are used to improve some symptoms such as self-mutilation, aggression, repetitive and stereotyped behaviors, distraction, hyperactivity, and sleep disorders [76]. Pangrazzi et al. (2020) summarized the importance of the role of the Omega-3, dietary polyphenols, and vitamin E/vitamin C/GSH network in the clearance of intracellular ROS in the disorders observed with ASD in their published review [77]. There are limited clinical and preclinical studies on oxidative biomarkers or behavioral effects of antioxidants in autism. Zambrelli et al. (2021) searched more than 20 articles focalizing on the effects of antioxidant supplementation on sleep in ASD. Most of the studies were about melatonin and also TRY, and the remaining studies were about luteolin, Coenzyme Q10, and quercetin, which are known to have important antioxidative effects. Although antioxidants have been reported to be beneficial in sleep problems in ASD, more studies have been suggested in this direction due to the limited number of studies [60]. Therefore, there is an urgent need for more comprehensive studies with large samples in this area.

10.4 Alzheimer's Disease

10.4.1 Oxidative Stress Biomarkers

AD is an increasingly common neurodegenerative disease characterized by cognitive and cognitive damage and many brain pathophysiologies due to dementia. AD is clinically diagnosed by neuroimaging methods and some cognitive tests and is also characterized by neuronal loss and neuropathologic lesions that occur in many brain regions [78]. Clinical symptoms such as hippocampal type episodic memory loss are observed in patients in the Prodromal/Predementia AD stage, but their daily living activities are not affected yet and they are used for the early symptomatic, predementia stage because they cannot fully diagnose dementia. Detection of biomarkers at these stages is challenging, and even at earlier stages, it is difficult to detect clinical symptoms. However, in its later stages, the presence of biomarkers from CSF or imaging may prove the pathology of AD [79]. AD progression is dependent on the stage and age of the individual, with varying rates of decline in clinical markers such as cognitive, neuroimaging, and biological [80]. The most common biodiagnostic markers for AD are the 42 amino acids amyloid β (β-amyloid 1-42), neurofibrillary tangles, and hyperphosphorylated protein tau. However, these

markers appear at later stages of the disease and are very costly [81]. The discovery of new biomarkers for AD with which we can understand the disease in its early stages is very important.

There is evidence that Amyloid plaques (Aβ) accumulate in the interneuronal space and cause oxidative damage. In addition, the accumulation of heavy metals in these regions may increase the effects of oxidative stress as the effect of plaques, especially metal ions such as copper and zinc. ROS production is triggered as the sensitivity to Aβ metal ions increases [82]. Oxidative stress damage may also occur in cases such as selenoproteins and Se accumulation. It can trigger the aggregation of Aβ plaques by stimulating hyperphosphorylation of the tau protein, resulting in neuronal toxicity and neurodegeneration (in Fig. 10.2) [83]. In the neural mechanism, redox metals such as Cu, Fe, and Hg can also cause such situations and can stimulate neuronal apolipoprotein E receptor-2 (ApoER2) by increasing signaling in AD [84]. The increase in microglial cells against interneuronal Aβ, which occurs in the pathogenesis of AD, unfortunately, affects the number of astrocytes that feed the neurons. In addition to this resulting inflammatory response, NO synthesis can be induced and cause a regional cytokine (eg TNF-a, IL-1p, IL-6) storm [85]. Meanwhile, Aβ causes dysfunction in mitochondria while triggering ROS

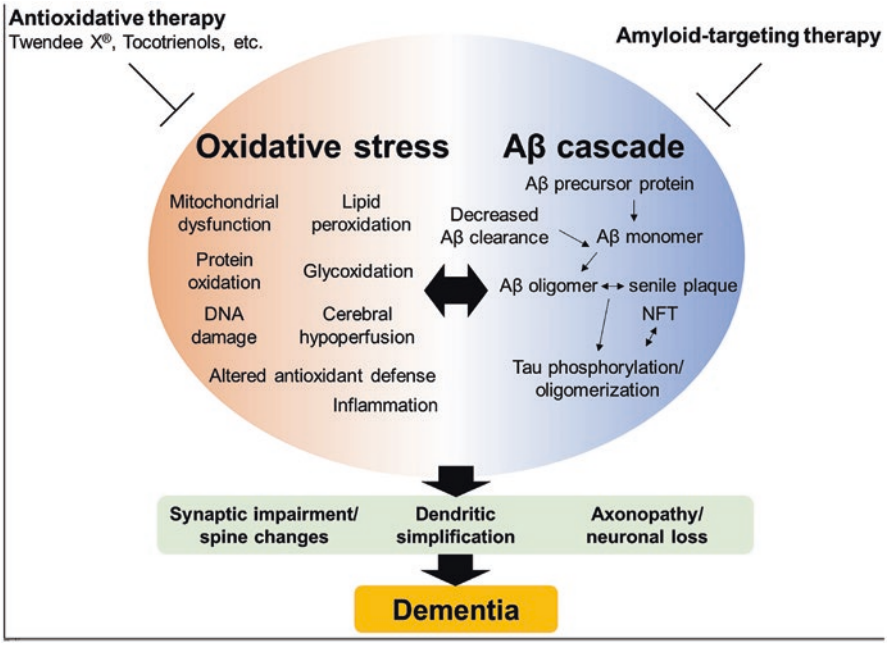

Fig. 10.2 Oxidative stress may develop in AD disease associated with Aβ accumulation. Mitochondrial dysfunction, protein oxidation, DNA damage, and lipid peroxidation develop as a cause/result of this situation, resulting in axonopathy, dendrite pruning, and synapse deficiency. Antioxidative agents such as Twendee X® and tocotrienols are currently available to prevent such situations [83, 89]

production via NADPH oxidase activation in microglia and astrocyte cells, causing oxidative damage [86, 87]. Oxidative damage in AD may have markers on cell membranes (lipid peroxidation), post-translational protein changes, and the production and function of genetic materials [88].

The current systematic review suggested that lipid peroxidation is the most potential oxidative stress marker in the diagnosis of AD due to its high lipid content and specificity in the brain [90]. Similarly, in another systematic review, although the included studies reported that the serum ratio of lipid peroxidation was high in the patients' sera, it was stated that there would not be sufficient evidence for the follow-up of treatment for AD and its evaluation as a complete biomarker [91]. Uruno et al. (2020) found that decreased GSH levels were increased by Nrf2 induction model $Keap1^{FA/FA}$ mice. The authors proposed a novel plasmalogen-phosphatidylethanolamine (PlsPE) level as the biomarker of AD [92]. These results suggest that Nrf2 overstimulation may ameliorate cognitive disorder in the AD mouse model by protecting them from both oxidative stress and neuroinflammation, and suggesting that Nrf2 is indeed an important therapeutic target of AD. The levels of 8-OHdG in the CSF of AD patients were found to be quite high compared to healthy controls, associated with impaired DNA repair [93]. In general, commonly reported oxidative stress biomarkers of AD are ApoE genotype, GSH/GSSG, MDA, coenzyme Q10, 8-OHdG, SOD, H_2O_2, GPx, and isoprostanes [90]. Consequently, as metalized AB is one of the major drivers of ROS production in the brain, the peptide itself is often attacked and oxidized by ROS activity, so it may appear as a very specific oxidative stress biomarker for AD [94].

Finally, there is a new research area that some microRNAs (miR) may relate to oxidative stress in AD. Kou et al. (2017) reported that miR-34a can increase APP accumulation in AD pathophysiology by suppressing oxidative stress associated with autophagy inhibition followed by mitochondrial damage [95]. miR-141-3p is detected at low levels in plasma exosomes of AD patients and mouse memory loss due to miR125b-5p overexpression [96] likewise miR-141-3p was found at high levels in mediator exosomes of astrocyte cells in the brain [97] and a recent study found that miR-125b-5p can weaken oxidative stress after Aβ-inducement [33]. However, another study reported that miR-125b-5p diminished the ROS levels and decreased mitochondrial membrane potential, and showed a neuroprotective effect against oxidative stress [98]. Although exosome-mediated or free miRNA levels have been investigated in many neurodegenerative diseases until now, it can be clearly said that especially for the oxidative process, many mysteries that need to be clarified in this area continue.

10.4.2 Antioxidative Treatments

Clinical trials based on the hypothesis that AD pathology is neurodegeneration as a result of amyloid-beta (Aβ) and progresses from hippocampal destruction to the brainstem, with dire outcomes initially led to new therapeutic research for disease

control, but unsuccessful trials proved that this hypothesis was the result, not the cause of the disease [99]. Currently, the applied treatments only ease the symptoms and temporarily lessen the cognitive progression rate of AD symptoms. Considering the situations given in the section on antioxidant biomarkers, the importance of antioxidative approaches cannot be ignored. Naturally-sourced approaches are promising. In many reviews, Brahmi (Bacopa monnieri), Quercetin and *Ginkgo biloba* are among the traditional "anti-dementia treatments" and the importance of their neuroprotective and antioxidant effect is emphasized, Dubey ve Chinnathambi (2019), Khan et al. (2019), Singh et al. (2019) and Noori et al. (2021) published a review for many natural products that have antioxidant and neuroprotective effects on AD [100–103].

There is a lack of evidence for the use of probiotics. Athari Nik Azm et al. (2018) reported a decline in the accumulation of Aβ, neuroinflammation, and oxidative parameters in an Alzheimer's-probiotic supplementation (Lactobacilli and Bifidobacteria) group which was an β-amyloid (1–42) injected rats [104]. Kobayashi et al. (2017) also demonstrated that the introduction of *Bifidobacterium breve* strains A1 in an AD mouse model has inhibited hippocampal inflammation and oxidative stress-related gene expression [105]. Den et al. (2020) also supported the previous studies' reports with randomized controlled trials. They found that probiotics have improved cognitive performance in AD or Mild cognitive impairment (MCI) patients, maybe because of reducing both inflammatory and oxidative chemical levels [106]. These results suggest that probiotics may have many advantages because of their anti-inflammatory and antioxidant effects.

There are some studies on antioxidant therapy. These antioxidants mainly contain their substrates or coenzymes, various endogenous antioxidant enzymes, and non-enzymatic antioxidants, as well as natural and synthetic antioxidant sources that maintain the redox balance in the biological system [107]. Chen et al. (2020) reported a synthetic chalcone derivative and 2-Hydroxy-40-methoxychalcone decreased ROS activity, induced Nrf2 pathways, enhanced GSH levels, and anti-inflammatory agents, thus causing healing [108].

In another example, the authors showed the importance of the antioxidant effects of Proxison (belong to synthetic flavonoid groups) with improved cellular uptake, free ROS and RNS scavenging power, and neuroprotective action against the cell in a zebrafish animal model [109]. In the results of Systematic Review and Meta-Analysis on vitamins, other antioxidant components including a single antioxidant supplement such as vitamin C, vitamin E, or mixtures thereof did not clearly show a therapeutic effect on cognitive decline in AD [110, 111]. Twendee X (TwX) is an important supplement in AD disease containing 8 antioxidants. A multicenter, randomized, double-blind, and placebo-controlled prospective interventional study, reported that the use of TwX for 6 months increased cognitive functions in MCI patients, but did not affect their daily living activities [83]. In general, it has been seen that such antioxidants are emphasized in the literature and that biomarker studies should be increased for new therapies to be developed.

10.5 Conclusion

Recently, extensive clinical and preclinical studies of oxidative stress biomarkers of AD, ASD, and schizophrenia have provided strong evidence that they play a role in both the etiology and course of these diseases. Lipid peroxidation levels were particularly promising for the potential oxidative stress biomarker and Probiotic supplement has positive contributions to both cognitive and oxidative stress in AD. Although the results of the levels of oxidative stress biomarkers related to schizophrenia and ASD are controversial, more studies are needed in the future. However, the effects of NAC supplementation on schizophrenia symptoms and markers cannot be ignored. The findings of regulating the antioxidant balance of antidepressant, anxiolytic or antipsychotic drugs used in the clinic for AD and schizophrenia have been reported, and the promising aspects of supplements/combined therapies with antioxidant effects in all three diseases are highlighted. However, many important issues remain to be fully elucidated, and more preclinical and clinical studies are needed to evaluate the precise contribution of oxidative stress in psychiatric disorders.

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