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Antioxidants as a Preventive Treatment for Epileptic Process: A Review of the Current Status

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Abstract: Epilepsy is known as one of the most frequent neurological diseases, characterized by an enduring predisposition to generate epileptic seizures. Oxidative stress is believed to directly participate in pathways leading to neurodegeneration, which serves as the most important propagating factor, leading to the epileptic condition and cognitive decline. Moreover, there is also a growing body of evidence showing the disturbance of antioxidant system balance and consequently increased production of reactive species in patients with epilepsy. A meta-analysis, conducted in the present review confirms an association between epilepsy and increased lipid peroxidation. Furthermore, it was also shown that some of the antiepileptic drugs could potentially be responsible for additionally increased lipid peroxidation. Therefore, it is reasonable to propose that during the epileptic process neuroprotective treatment with antioxidants could lead to less sever structural damages, reduced epileptogenesis and milder cognitive deterioration. To evaluate this hypothesis studies investigating the neuroprotective therapeutic potential of various antioxidants in cells, animal seizure models and patients with epilepsy have been reviewed. Numerous beneficial effects of antioxidants on oxidative stress markers and in some cases also neuroprotective effects were observed in animal seizure models. However, despite these encouraging results, till now only a few antioxidants have been further applied to patients with epilepsy as an add-on therapy. Based on the several positive findings in animal models, a strong need for more carefully planned, randomized, double-blind, cross-over, placebo-controlled clinical trials for the evaluation of antioxidants efficacy in patients with epilepsy is warranted.

Keywords: Antiepileptic drugs, antioxidants, epileptogenesis, meta-analysis, neuroprotective, oxidative stress, reactive species.

1. INTRODUCTION

Epilepsy is a neurological disease, characterized by an enduring predisposition to generate epileptic seizures and by enormous neurobiological, psychological, cognitive, and social consequences. Repeating seizures originate from hyperexcitation of certain group of neurons and lead to different transient clinical signs and laboratory findings. The crucial role in the disease development has the formation of the epileptogenic focus which has an uncontrolled hyperexcitability due to partial prolonged depolarization of cellular membranes [1]. Prolonged depolarization is the result of imbalance in neuronal system polarization in favour of hyperpolarizing influences as a consequence of enhanced excitation, decreased inhibition and/or diverse nervous system changes. This represents the underlying mechanism of the initiation and propagation of a seizure in a normal individual [2]. There is evidence that the formation of reactive species or the decreased activity of antioxidant systems may result in different forms of epilepsy as well as increased chances of repeating epileptic seizures [1].

Regardless, the abundance of antiepileptic drugs (AEDs) introduced after phenobarbitone (PB) in the beginning of the previous century, nowadays 20-30% of patients with epilepsy still continue having seizures [3]. These patients require a more aggressive approach, since monotherapy fails to control seizures. However, even polytherapy is not always effective. Furthermore, the incidence of adverse reactions, namely neurological disruptions, psychiatric and behavioural changes, as well as metabolic alterations is also increasingly important. Therefore, there is an urgent need for better tolerated and more efficient AEDs, especially in this group of patients [4].

Furthermore, during metabolic processes, numerous AEDs, especially from the older AEDs generation, including PB, phenytoin (PHT), carbamazepine (CBZ) and valproic acid (VPA), produce reactive metabolites which can covalently bind to different endogenous macromolecules or increase the formation of reactive oxygen species (ROS) that can induce oxidative damage and cause toxicity. To support this theory, numerous studies evaluating the influence of epilepsy and AEDs on the formation of free radicals, show that either of them could be connected to oxidative stress generation [1, 5-9].

Therefore, this review summarizes the rationale for use of antioxidants as add-on therapy for modulating free radical mediated oxidative stress in epilepsy and evaluates the existing studies investigating the efficacy of different antioxidant therapies.

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2. OXIDATIVE STRESS AND ITS ROLE IN EPILEPTOGENESIS

Oxidative stress is a consequence of the increased oxidant burden which overwhelms the endogenous antioxidants and repair capacity or a consequence of diminished endogenous antioxidants and repair capacity which cannot encompass the normal oxidant burden [10]. Glutamate, which act as excitatory central nervous system (CNS) neurotransmitter and could potentially act excito-toxic, especially at higher concentrations, is believed to be one of the key factors involved in oxidative stress generation [11].

Increased formation of ROS results in elevated intracellular Ca^{2+}concentration, which is seen in neuroplasticity changes, as well as seizure-induced neuronal death either through necrosis or apoptosis [12]. Increased intracellular Ca^{2+}, which persist even through the chronic phase of epilepsy and is therefore crucial for the continuation of recurrent seizures, can influence on GABA A receptor recycling and thus alter neuronal excitability [13]. Moreover, increased intracellular Ca^{2+}can change gene transcription, protein expression and turnover, neurogenesis, neuronal sprouting, and others cell physiological functions [14].

Epileptogenesis is defined as the process in which an initial CNS insult leads to the onset of the epileptic condition as well as to the propagation of events that occur after established epilepsy and can take years or even decades [15]. This supports the theory that sequence of changes after an initial insult is essential for the development of the epileptic condition [16, 17]. Although, the process of epileptogenesis is so far not clearly understood [18], the above mentioned neuronal cell death is believed to be one of the most important factor that could lead to the development of the epileptic condition [16].

Oxidative stress is known as a fundamental cytotoxic mechanism involved in pathogenesis of various neuro-degenerative diseases [19]. Its role in neurodegenerative diseases is especially important, because cells in the CNS, namely neurons, are particularly vulnerable to the destructive effects of reactive species [2]. ROS can cause deleterious effects on cells through acting on signalling pathways or through causing nonspecific oxidative damage to bio-macromolecules [10]. Generally, biological effects of ROS are successfully controlled by endogenous defence system of antioxidant enzymes (glutathione reductase -GR, glutathione peroxidase -GPx, superoxide dismutase -SOD, and catalase -CAT) and non-enzymatic antioxidants (namely glutathione -GSH, vitamin E, vitamin A, vitamin C and β-carotene) [20]. Antioxidant enzymes block the initiation of reactive species chain reactions, while the non-enzymatic antioxidants react directly with reactive species and thereby prevent the propagation of chain reactions [20]. A major source of ROS is the respiratory chain reaction, which takes place in cell mitochondria [21, 22].

Therefore, any changes in oxidative burden in favour of prooxidants can lead to initiation or propagation of already established epileptic seizures by proposed mechanisms that provoke neuronal cell death.

3. INFLUENCE OF OXIDATIVE STRESS ON BIOLOGICAL MACROMOLECULES

Free radicals, resulting from endogenous redox imbalance, are believed to play an important role in causing oxidative stress, cell death and consequently tissue damage. They are able of injuring different cell macromolecules, namely lipids, nucleic acids, proteins, and carbohydrates, finally leading to cell death and cognitive decline, as described in our previous work [2].

Since oxygen is lipophilic and therefore accumulates in higher amounts in biological membranes and since polyunsaturated fatty acids (PUFAs) in lipoproteins and phospholipids are especially vulnerable to oxidative injuries, the major consequence of increased oxidative stress reflects in lipid peroxidation. Lipid peroxidation disturbs biological membranes and is therefore particularly destructive to their structure and function. Moreover, several by-products are produced through lipid peroxidation, including unsaturated hydroperoxides, which can further break down to generate diverse reactive aldehydes. Through covalent binding to cellular proteins, reactive aldehydes can further alter their function and subsequently provoke cellular damage. One of the widely studied reactive aldehydes is malondyaldehyde (MDA). Moreover, peroxidation products, known as peroxyl radicals, are less reactive compared to ROS and have therefore longer time of action. Consequently, they are able to diffuse more distant, even through cells, where they can react with other cellular constituents and cause diffuse cellular damage. Due to greater stability, peroxidation end products are valuable laboratory markers. General laboratory markers of lipid peroxidation are MDA and F2-isoprostanes [23, 24].

Free radicals may further trigger disruption of nucleic acids. They can break deoxyribonucleic acid (DNA) strands or directly modify bases, which leads to deletions and other mutations. These modifications could result in aberrant gene expression and even cell death [25]. DNA damage activates the DNA repair enzyme poly-ADP-ribose polymerase-1, which over activation depletes its substrate, nicotinamide adenine dinucleotide, slowing the rate of glycolysis, electron transport, and ATP formation, eventually leading to functional impairment or cell death [26]. General laboratory marker of oxidative DNA damage is 8-hydroxy-2-deoxyguanosine (8-OHdG) [27].

The mitochondrial DNA (mtDNA), is even more vulnerable target for free radical damage because of diminished repair mechanisms and lack of histones and because it is situated much closer to the site of ROS generation. MtDNA disruption may lead to mitochondrial dysfunction that might result in disturbed cell function. Consequently disturbed electron transport chain and additional ROS production can result in a potentiation of oxidative stress [17]. After all, the most susceptible to oxidative damage is ribonucleic acid (RNA), since it is single stranded, not protected by hydrogen bonding, and less protected by proteins. RNA damages may result in errors in proteins or dysregulation of gene expression [28].

Moreover, free radicals can oxidize both the backbone and side chains of proteins [23]. These oxidative modifications

may disturb the function of enzymes, receptors, neurotransmitters, and structural proteins [29]. One of the most commonly used methods to quantify protein oxidation is by measuring the protein carbonyl level [23].

Finally, oxidation of monosaccharide sugars results in the formation of oxaldehydes, which can contribute to protein aggregation. The term advanced glycation end-product (AGE) describes either protein damage that results from adduction of reducing sugars and subsequent oxidative evolution, or adduction of more reactive sugar oxidation products, termed glycoxidation. Oxidation of carbohydrate polymers may cause depolymerization and disturbed function of the involved polymers. AGEs are known as useful markers of oxidative damage [30].

4. OXIDATIVE STRESS IN DRUG-NAIVE PATIENTS WITH EPILEPSY

Changes in antioxidant defence mechanisms, as a result of epileptic condition itself or the effects of antiepileptic therapy have been studied in humans, but the observed research findings are discordant [5-7, 31-47].

The majority of studies confirmed impaired oxidative status in untreated patients with epilepsy in terms of elevated lipid peroxidation reflected in elevated MDA levels [1, 33, 37, 42, 44, 46, 47], and significantly decreased serum total antioxidant capacity [7, 32, 44]. Studies further reported elevated [32, 35], decreased [43, 46] or unchanged [31, 37] SOD activity, elevated [31], unchanged [32, 37, 44] or decreased [36] GPx activity, unchanged [31] or decreased [37] GR activity and unchanged CAT activity [43]. Arhan *et al.* observed also significantly elevated nitric oxide (NO) levels in patients with epilepsy in contrast to healthy controls [45].

Although, MDA levels are elevated in most cases, unchanged [31, 43, 45] or even decreased [32] levels were also reported. In a study designed by Yis *et al*., it was shown that scavenger systems are activated in order to decrease lipid peroxidation, resulting in lower erythrocyte MDA levels and slightly, insignificantly higher SOD activities [32].

To evaluate the influence of epilepsy on oxidative status, we performed a meta-analysis on studies of lipid peroxidation reflected in MDA levels. A selection criterion for inclusion of the study was the comparison of untreated patients with confirmed epilepsy with a control group, presented by healthy control matches. Eleven studies were found which met the inclusion criteria [1, 31-33, 37, 42-47].

Weighted mean difference (WMD) with 95% confidence interval (95% CI) was calculated from the extracted data, using Review Manager 5.2 (The Cochrane Collaboration, Oxford, UK). Due to heterogeneity of the results of various studies, random effect model was applied. WMD of the MDA levels was 0.90 μg/mL (95% CI 0.35 to 1.46) suggesting increased lipid peroxidation in epilepsy (Fig. **1**).

5. OXIDATIVE STRESS IN PATIENTS WITH EPILEPSY TREATED WITH THE OLDER GENERATION OF AEDS

Oxidative stress is known to be present in epilepsy as a cause or/and a consequence of epileptogenesis process. Furthermore, it was also shown that long-term treatment with AEDs can cause elevated free radical production in neuronal cells and consequently increased oxidative damage, leading to neurodegeneration. Several conventional AEDs are known to be extensively metabolized in the body. Through their metabolic transformation, numerous reactive metabolites, which are capable of covalent binding to biological macromolecules, are formed. Thus, the AEDs may, besides their main inhibitory activity on the epileptic focuses, also provoke systemic toxicity, either through increased oxidative damage or covalent binding of their reactive metabolites to biological macromolecules [8, 9, 48, 49]. Hence, it is of particular importance to find out the impact of AEDs on oxidative stress.

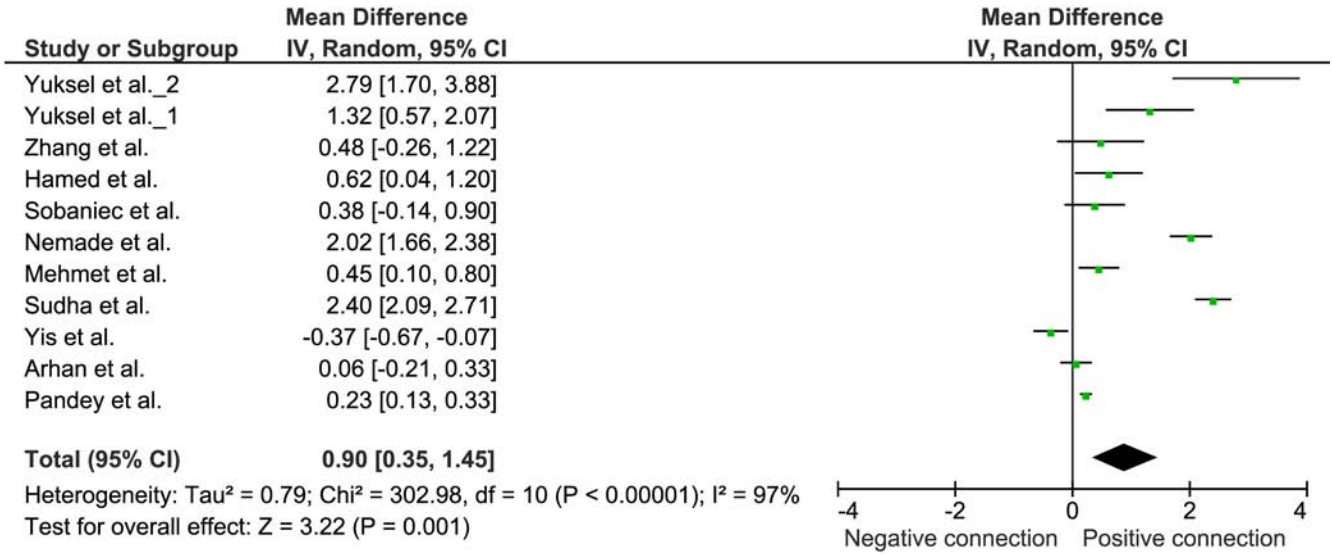

Fig. (1). Meta-analysis of the studies comparing the lipid peroxidation in untreated patients with epilepsy and healthy controls. The difference in plasma MDA concentration (μg/mL) in a group of untreated patients with epilepsy and a healthy control group.

5.1. Valproic Acid

Most studies have shown increased lipid peroxidation in children and adolescents [1, 31-33, 43, 45, 49] or adults [44] treated with VPA compared to untreated patients with epilepsy [1, 32, 33, 43-45] or healthy controls [1, 31, 33, 49]. Schulpis reported also decreased total antioxidant capacity levels [49]. Studies further showed decreased [50] or unchanged [5, 31, 51] SOD activity, elevated [44], unchanged [5, 31] or decreased [50, 52] GPx activity, elevated [52] or decreased [31] GR activity, unchanged [51] CAT activity and elevated [44] or decreased [52] serum Se levels. Furthermore, Schulpis in children and Varoglau, in adults found elevated 8-OHdG levels indicating increased DNA damage [49, 53]. On the other side, Peker *et al.* reported slightly higher NO concentrations in VPA group, however no significant differences in serum MDA levels were detected [51].

5.2. Carbamazepine

In the case of CBZ influence on lipid peroxidation inconsistent results were found. Some studies have shown increased oxidative stress expressed as lipid peroxidation [7, 33, 44, 53], some have shown ambiguous changes [1, 6] and the others decreased [31, 42] lipid peroxidation compared to untreated patients with epilepsy [1, 6, 31, 33, 42, 44] or healthy controls [7, 53]. Hammed *et al.* confirmed also decreased total antioxidant capacity [44]. Studies further reported elevated [6, 33], decreased [50] or unchanged [1, 5] SOD activity, elevated, unchanged [1, 5] or decreased [44, 50] GPx activity, unchanged or decreased GR activity, decreased CAT activity [50] and serum Se levels [44]. Moreover, Varoglau *et al*. found elevated 8-OHdG levels in adult patients with epilepsy, indicating increased DNA damage [53]. Niketić *et al*. further reported elevated levels of Hb ASSG, representing a glutathione adduct of haemoglobin (Hb). Occurrence of Hb ASSG serves as a marker of oxidative stress in erythrocytes [50]. A study, conducted by Yuksel *et al*., determined the modifications in the antioxidant system in children with epilepsy receiving long-term AEDs [1]. The results showed no significant differences in lipid peroxidation, SOD and GPx activities in children with epilepsy on CBZ monotherapy in contrast to the healthy controls and untreated patients with epilepsy [1]. The levels were re-tested two years after the beginning of the treatment when increased lipid peroxidation and decreased SOD and GPx activities were noticed compared to healthy controls. SOD activity was lower even compared to untreated patients with epilepsy [33].

5.3. Phenobarbitone

Aycicek *et al*. investigated the effect of PB on different serum markers of oxidative stress. They examined the oxidative stress index, total antioxidant capacity, lipid hydroperoxide, total peroxide, and concentrations of individual serum antioxidants such as albumin, bilirubin and uric acid. Apart from increased oxidative stress index and lipid hydroperoxide in the group treated with PB in contrast to control group, no other significant changes were observed [7]. Furthermore, Niketić *et al.* observed decreased levels of SOD and GPx in adults treated with PB [50].

5.4. Polytherapy with Carbamazepine and Valproic Acid

In a large group of children and adolescents with epilepsy, receiving CBZ and VPA polytherapy, increased MDA concentrations and therefore lipid peroxidation were seen compared to healthy controls. Decreased SOD activities and significantly increased GPx activities were found in comparison to relevant levels in the healthy controls. Moreover, it was found that GR activity was slightly lower in polytherapy as well as in VPA monotherapy compared to healthy control. On the other hand, GR activity was higher in CBZ monotherapy group [31].

5.5. Meta-analysis

To explore the influence of AED therapy on oxidative status, a meta-analysis evaluating the influence of VPA and CBZ on MDA levels was designed. A selection criterion for inclusion of the study was the presence of a group of patients with epilepsy on therapy with VPA or CBZ and a control group of untreated patients with epilepsy. Seven [1, 31-33, 43-45] and six [1, 6, 31, 33, 42, 44] studies were found which met the inclusion criteria for VPA and CBZ, respectively.

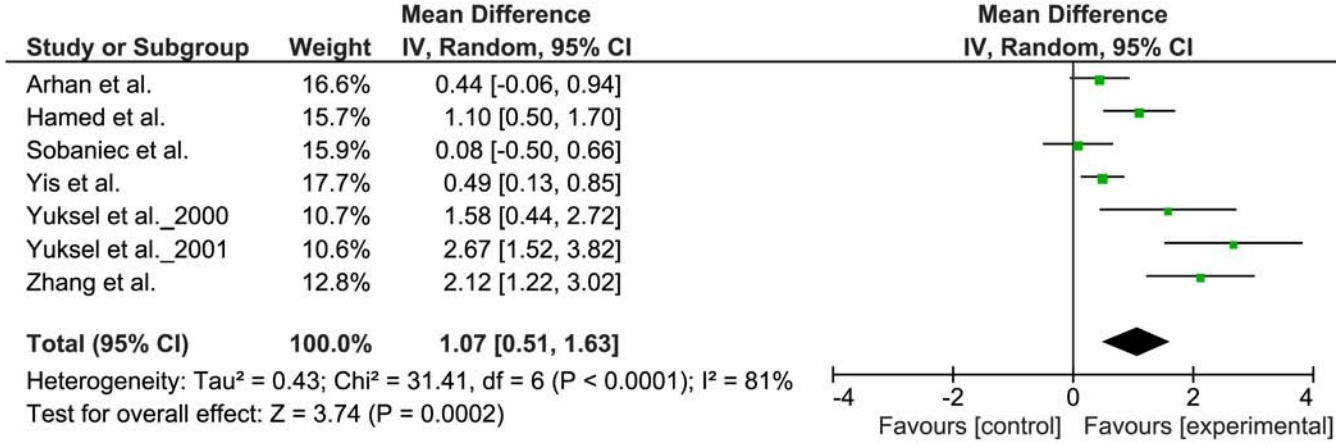

Fig. (2). Meta-analysis of the studies comparing the lipid peroxidation in patients with epilepsy, treated with VPA, and a control group of untreated patients with epilepsy. The difference in plasma MDA concentration (μg/mL).

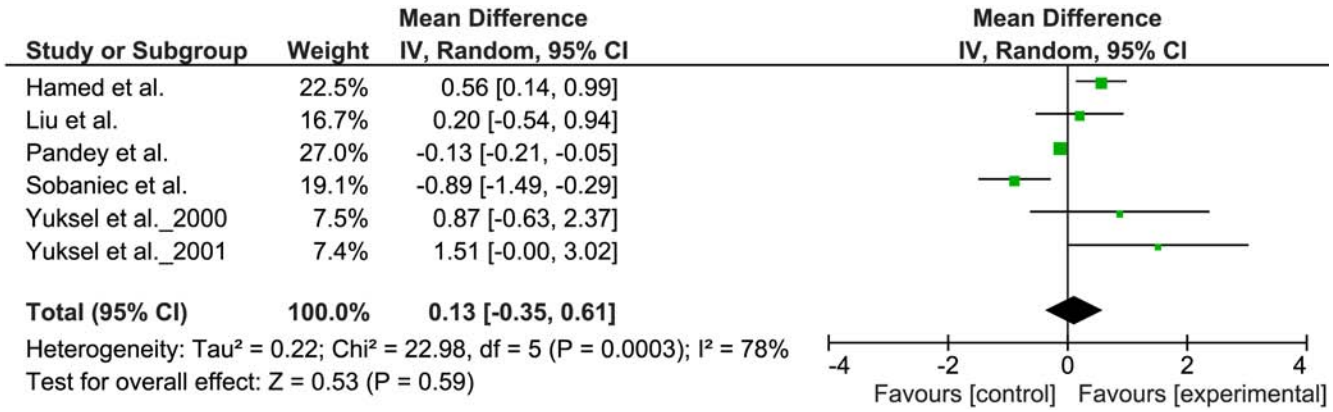

Fig. (3). Meta-analysis of the studies comparing the lipid peroxidation in epilepsy patients treated with CBZ and a control group of untreated patients with epilepsy. The difference in plasma MDA concentration (μg/mL).

WMD with 95% confidence interval (95% CI) were calculated from the extracted data. Due to heterogeneity of the results of various studies, random effect model was applied. WMD of the MDA levels were 1.07 μg/mL (95% CI 0.51 to 1.63) in the case of VPA (Fig. **2**) and 0.13 μg/mL (95% CI - 0.35 to 0.61) in the case of CBZ (Fig. **3**).

Significantly increased MDA levels in VPA treated group were found, while in CBZ group the effect of treatment on MDA level was inconclusive. Increased MDA levels seen in VPA may be a consequence of afore mentioned conventional AEDs metabolism and subsequent elevated free radicals formation, causing numerous side effects [1, 48, 54]. Similarly, numerous studies have confirmed increased lipid peroxidation in older generation AEDs like PB [7], PHT [6] and already mentioned CBZ [44]. These drugs represent classical aromatic AEDs which have also been proven to provoke oxidative stress either alone or through their metabolites [55]. This free radical generation could be the reason for numerous side effects and even for the failure of seizure control. Unfortunately, there are sparse studies evaluating the effect of newer AEDs on oxidative status to perform reliable meta-analysis. However, there are few studies performed on newer AEDs generation which have shown better oxidative profile. Studies evaluating oxcarbazepine [34, 45], topiramate [56] and lamotrigine [57] have shown decreased lipid peroxidation compared to untreated patients with epilepsy or healthy controls.

These results confirm that in patients with epilepsy the oxidants-antioxidants balance is largely modified by epileptic condition as well as by antiepileptic therapy. Therefore, further research is needed, especially with the newer AEDs.

6. ANTIEPILEPTIC THERAPY AND OXIDATIVE STRESS

6.1. Medication Therapy

Despite better understanding of the pathophysiological processes related to seizure initiation and propagation in the brain, and despite the introduction of several newer, second and third generation AEDs, there are still 20-30% of patients with epilepsy that are inadequately treated with the recent frontline AEDs [58, 59]. Most of these patients have focal epilepsies, which may be caused by brain trauma, brain tumors, complicated febrile convulsions, status epilepticus (SE) or ischemic lesions. As a consequence of such pathological processes a neural cell loss can be found in areas of epileptogenesis. Progressive neuronal cell loss is believed to have a major role in development of the resistant forms of epilepsy, such as temporal lobe seizures and further more even in development of the resistance to AED therapy at later stages of the disease [60].

Combination of two or more first- or second-generation AEDs or the application of novel third-generation AEDs are the most appropriate, but still often not sufficiently effective therapeutic options when surgical treatment cannot be offered [58, 61-63]. While oxidative stress is believed to have an important function in epilepsy, approaches covering neuroprotective as well as anticonvulsive actions are desirable. Use of AED zonisamide with independent neuroprotective and antiepileptic activity in drug resistant patients with epilepsy, has confirmed this theory [64, 65].

6.2. Add-on Therapy with Antioxidants

Currently, ROS generation is believed to represent one of the crucial processes, which underlies the mechanism of causing damaging effects on brain by epileptic activity. The resulting neuronal alterations in the brain circuitry represent the fundamental changes which could eventually lead to a condition of recurrent spontaneous seizures. Therefore, neuroprotective actions could slow or even prevent epileptogenesis, hence, decrease seizure severity and frequency, improve established AED therapy efficacy and reduce well known AED pharmacoresistance [66-69].

Since the neutralisation of the increased ROS formation during seizures depends on the ability of the antioxidant defence systems, the antiepileptogenic therapeutic potential of various substances possessing antioxidant activities, have been extensively studied [67-69]. This includes endogenously present antioxidants, such as α -lipoic acid [70-73], GSH [74], melatonin [75-85], ubiquinone (coenzyme Q_{10}) [86, 87] and vitamin A [88], exogenous anticonvulsive and neuroprotective substances, such as α-tocopherol [53, 70-72], ascorbic acid [66, 89, 90], curcumin [91-100], N-acetylcisteine [101], omega-3 fatty acids [102-112] and resveratrol [113,

114], and novel synthetic, potent radical scavengers, like aspalatone [115], EPC-K1 [116], EUK-134 [117], MnTBAP [118-120], and tempol [121]. These compounds, generally defined as molecules with the ability to quench or reduce highly ROS, exerts neuroprotective effects and can therefore protect the brain against oxidative stress as seen in some experimental models of seizures [66, 70-74, 90-92, 96, 99, 122-125].

It is known that conventional AEDs fail to sufficiently control seizures. Furthermore, long-term use of these AEDs significantly increase oxidative stress and predispose to cognitive impairment [86]. The reason for seizures and cognitive deficit could lie in the inability of the current AEDs to establish the balance between oxidants and antioxidant defence mechanisms in the body [91]. Apart from epilepsy itself causing oxidative stress, increased oxidative stress triggered by AEDs is also suggested to contribute to the induction of seizures and cognitive impairment in patients with epilepsy [25, 37, 44, 91]. Therefore, the capability of antioxidants to inhibit seizure generation and decreased oxidative stress markers, further support their significant role as having supposed antiepileptic potential [126].

There is relatively sparse data regarding clinical activity of AEDs on cognitive impairment. Some AEDs, namely PB, VPA and CBZ have been shown to significantly disrupt the vital balance between oxidants and antioxidants [7, 43, 44]. CBZ and lamotrigine have also been shown to trigger an important decline in learning and memory tests [127]. To confirm these findings, significant cognitive decline after CBZ treatment has been reported in newly diagnosed patients with epilepsy [128]. Furthermore, Reeta *et al*. reported that PB and CBZ caused significant oxidative stress and therefore deterioration of learning and memory in rats after 21 days of treatment. PB caused more cognitive impairment compared to CBZ [91]. Comparable trends have been already reported in humans [129, 130]. Finally, it has been reported that PB, PHT and VPA can trigger deleterious effects on the immature brain, which can in some cases lead to severe deterioration of cognitive functions development [91].

According to mentioned above, the use of antioxidants as add-on therapy offers a potentially beneficial way of treatment in order to provide neuroprotective environment in the injured or stressed brain. Potential benefits of antioxidants, used as add-on therapy, were extensively studied in different *in vitro* or *in vivo* animal models of seizures and epilepsy and in patients with epilepsy. The results and observed potential mechanisms of their anticonvulsive action are further described in details and summarized in Tables **1**-**3**.

6.2.1. Endogenous Antioxidants

α-Lipoic Acid

α-Lipoic acid (LA) is an important cofactor for mitochondrial enzymes and an essential natural antioxidant [70].

Pre-treatment with LA demonstrated decreased nitrite content and lipid peroxidation level, while increased SOD, CAT, and GPx activities in striatum were observed during the acute phase of seizures induced by pilocarpine in adult rats [70, 131, 132]. A reduction in free radical formation and an increase in the activity of antioxidant enzymes produced an important enhancement in the resistance to seizures. Animals exposed to LA treatment presented no differences in physical growth and brain development, suggesting that LA ameliorates metabolic parameters only in a pilocarpine model [133].

It was further demonstrated that pre-treatment with LA is able to reduce brain oxidative metabolism and consequently prevent pilocarpine-triggered seizures, SE and mortality of adult rats. These findings support an important function of free radicals in managing seizures development, maintenance and propagation [70].

After all, as seen above, LA could serve as neuro-protective treatment against seizures induced by pilocarpine.

Melatonin

Melatonin is a pineal hormone with its main function of regulating circadian rhythm [134]. It exhibits potent antioxidant activities by direct scavenging of hydroxyl and other free radicals, by stimulating GPx activity, and by inhibiting NO synthase [135].

Melatonin was reported to suppress generalized seizures in amygdala kindled rats [75]. It is also known that pineal-ectomy reduces the number of stimulations required to trigger amygdala kindling [136]. Similarly, in the model of pilocarpine induced seizures in rats, pinealectomy was also found to be associated with reduced time needed to first spontaneous seizures and further even increased number of spontaneous recurrent seizures during the chronic phase [79]. These findings together confirm the neuroprotective role of melatonin, both endogenous and exogenous [136].

Simultaneous admission of melatonin and kainic acid (KA) was further shown to completely inhibits KA-induced seizures and reduces mitochondrial DNA damage in the mouse brain cortex. These observed neuroprotective and anticonvulsant activity of melatonin could be mediated by scavenging of hydroxyl radicals [76, 77]. Besides, melatonin has been also reported to reduce iron-induced seizures in rats through inhibition of peroxidation [135].

Experiments conducted in mice showed that melatonin significantly raised the electroconvulsive threshold, and increased the CBZ and PB protective activity against electroshock. Since, melatonin was shown to increase the number of [^{3}H] GABA binding sites in animal hippocampus, it is reasonable to assume that these observed melatonin actions can be related to increased activity of GABA-ergic system [78].

Furthermore, supplementation with melatonin during the SE period in the pilocarpine model has been shown to decrease apoptosis in different limbic areas [79]. Anti-convulsive effects of melatonin were also observed in penicillin-induced epileptiform activity in rats. Melatonin administered intra-cerebroventricularly delayed the on-set of epileptic seizures confirmed by electrocorticogram.

Table 1. Observed anticonvulsive and neuroprotective actions of endogenous antioxidants.

Substance	Cells/Animals/Humans	Seizure Model	References
Potential antioxidant actions			
α-Lipoic acid			
Anti-convulsive effects	Animal model (rats)	PIL	[79, 142]
Inhibits seizure activity and oxidative damage • decreases lipid peroxidation and inhibits nitrite formation • enhances the activity of antioxidant enzymes • abolishes changes of Na^+, K^+-ATPase activity induced by pilocarpine	Animal model (rats)	PIL/Iron	[70, 72, 143]
Influence on neuronal excitability and further on development and propagation of certain seizure types, namely through its antioxidant activity	*In vitro* & *in vivo* models	-	[144]
Strong antioxidant effects *in vivo* and *in vitro* • decreases ROS • temporary metal chelating • increases α-tocopherol and ascorbate recycling	*In vitro* & *in vivo* models	-	[144]
Dihydrolipoic acid			
Strong antioxidant effects *in vivo* and *in vitro* • decreases ROS • temporary metal chelating • increases α-tocopherol and ascorbate recycling	*In vitro* & *in vivo* models	-	[144]
Melatonin			
Attenuates seizure activity and neurodegeneration • increases latency to the appearance of the first seizure	Animal model (rats)	KA/PTZ/PIL	[76, 78, 139, 145]
Exerts antioxidant properties	Patients with epilepsy	Children	[146]
Exerts anticonvulsive and neuroprotective properties • decreases ROS and RNS production • blocks lipid peroxidation and nucleic acids oxidation • maintains GSH homeostasis and the GSH-related antioxidant enzyme system	Animal model (rats)	KA/Amig. kindl	[142, 75]
	Animal model (mice/rats)	KA/Iron	[145, 147]
	Animal model (mice)	KA	[76]
	Animal model (rats)	KA	[148, 149]
Protects against seizures and decreased LPO	Animal model (rats)	Iron	[147, 150]
Protects against oxidative stress • free radicals scavenging • stimulation of GPx activity • inhibition of NOS activity	Animal model (rats)	Iron	[135]
Suppress epileptic activity by inhibiting peroxidation	Animal model (rats/mice)	Iron/KA	[147, 151]
Selen			
Provides protection against reactive oxygen species induced damage • levels are lower in patients with epilepsy	Patients with epilepsy	Children	[36]
Ubiquinone			
Prevents cells from free radicals induced oxidative damage • decreases the extent of oxidative stress and consequently the severity of seizures	Animal model (rats)	PIL	[86, 87]
Potentiate the antiepileptic effects of PHT treatment • ameliorates oxidative stress and cognitive impairment caused by PHT	Animal model (rats)	PIL	[86]

BBB – blood brain barrier, CAT – catalase, GPx – glutathione synthetase, GSH – glutathione, KA – kainic acid, LPO- lipid peroxidation, NOS - nitric oxide synthase, PIL – pilocarpin, PHT – phenytoin, PTZ – pentylenetetrazol, ROS – reactive oxygen species, RNS – reactive nitrogen species, SOD - superoxide dismutase

This anticonvulsant activity can again be explained by increased activity of GABA-ergic system, induced by melatonin [80].

It was further seen that acutely administered melatonin considerably elevated the threshold for clonic convulsions triggered by pentylenetetrazol (PTZ) in mice [137]. In fact, melatonin prevented PTZ-induced glutamine and aspartate increases, while at higher doses, melatonin further decreases nitrite content in different brain areas, including the hippocampus [138]. Moreover, melatonin pre-treatment before PTZ administration in guinea pigs was reported to increase seizure latency, attenuate seizure severity, and lower the mortality rate [139].

Collectively, melatonin has shown numerous protective functions in various animal seizure models, therefore it seems a promising neuroprotective agent.

Ubiquinone

Ubiquinone is a potent antioxidant which reacts with ROS and therefore prevents cells free radicals induced oxidative damage, including mitochondrial membrane lipid peroxidation. Besides, ubiquinol, representing a reduced form of ubiquinone, is further capable of additional reduction in lipid peroxidation, since it has the ability of performing as a chain-breaking antioxidant and recycling of other antioxidants, namely α-tocopherol and lipoic acid [140, 141].

Recently, studies evaluating the neuroprotective effects of ubiquinone in rats' pilocarpin-induced epileptic model were performed [86, 87]. In pilocarpine group, an important increase in hydroperoxide concentration and GPx activity was reported, while there were no changes observed in SOD and CAT activities. On the other hand, in rat hippocampus of ubiquinone group, markedly decreased hydroperoxide content and elevated SOD, CAT and GPx activities were observed [87]. Overall, ubiquinone has been reported to decrease the extent of oxidative stress and consequently the severity of pilocarpine-induced seizures [86].

Furthermore, ubiquinone was reported to potentiate the antiepileptic effects of PHT treatment by amelioration of oxidative stress and cognitive impairment caused by chronic PHT therapy in pilocarpine-induced seizures in rats. Therefore, ubiquinone can be used as a safe and effective add-on therapy to conventional epilepsy treatment, both to reduce seizure severity as well as to protect against seizure-induced oxidative damage [86].

These results suggest that ubiquinone may exert significant neuroprotective actions which might be helpful in the treatment of neurodegenerative disorders [86, 87].

6.2.2. Exogenous Antioxidants

Ascorbic Acid (Vitamin C)

Ascorbic acid represents a classical, potent water-soluble antioxidant, which reduces harmful oxidants and therefore protects biological macromolecules from oxidation [152]. Its main function is direct scavenging of superoxide and hydroxyl radical [66]. Furthermore, ascorbic acid is crucial for other antioxidants recycling, especially for vitamin E and lipoic acid. Moreover, it also enhances SOD and CAT enzymes activities [66, 90].

The use of ascorbic acid in animal studies demonstrated the reduction of neuronal damage, triggered by free radicals, which are particularly elevated in inflammation processes and neurodegenerative disorders [66].

Histopathological studies on animals, which were pre-treated with ascorbic acid, prior to pilocarpine induced seizure, have revealed a significant 60% reduction in the frequency of hippocampal brain damage induced by seizures and 5-fold decrease in the area of hippocampal damage [66]. The ascorbic acid pre-treatment has been further shown to increase hippocampal SOD and CAT activities, increase in the latency to first seizures, suppression of behavioural seizure episodes, and decrease in lipid peroxidation, nitrite content, brain damage, SE, severity of hippocampal lesions, and mortality of rats in pilocarpine induced seizures [66, 90, 153]. These findings are a consequence of ascorbic acid free radicals scavenging abilities, which support its neuro-protective activity. Moreover, ascorbic acid could compensate for the reduction of GSH synthesis caused by nitrite and nitrate inhibition, and also for the loss of other endogenous antioxidants and antioxidant enzymes, including SOD and CAT [66].

Additionally, ascorbic acid was further reported to decrease or prevent epileptic seizures evoked by $FeCl_3$ [116] or penicillin administration [154, 155].

Curcumin

Curcumin possess antioxidative and anti-apoptotic properties [92, 156]. It acts as an effective scavenger of ROS and RNS, which leads to decreased lipid peroxidation, oxidative DNA damage, mitochondrial dysfunction, and apoptotic cell death [93, 94]. Therefore, in experimental animal models, curcumin has been shown to exhibit protective effects against seizures, oxidative stress and cognitive deterioration in a dose-dependent manner [93, 96].

Curcumin pre-treatment was shown to prevent hippocampal neuronal cell death [92]. Precisely, curcumin, manganese complex of curcumin, and diacetylcurcumin treatment have been shown to attenuate hippocampal cell death induced by KA both, by inhibiting cell apoptosis as well as increasing neuroprotection accomplished through maintenance of intact blood brain barrier function [95, 96].

In PTZ animal models, curcumin expressed dose-dependent protection against seizures. It considerably extended latency phases presented before myoclonic, clonic and generalized tonic-clonic seizures occurred, and further decreased duration of generalized tonic-clonic seizures [96]. Furthermore, curcumin administration in rats inhibited brain MDA levels to increase, indicating a decreased lipid per-oxidation [157]. Additionally, a recent study of curcumin supplementation in PTZ kindled rats confirms antioxidant effect of curcumin through a decrease in MDA, and an increase in CAT and glutathione S-transferase levels observed in rat brain [100].

Curcumin pre-treatment in rats was further shown to poses protective effects against oxidative stress and cognitive deterioration induced by PHT [99] as well as against seizures in animal experimental models of epileptic seizures induced by iron administration [97] or electroshock [98].

Co-administration of curcumin with PHT, PB and CBZ showed a significant improvement in elevated plus maze test as well as in passive avoidance paradigm [91, 99, 158]. These two tests are often used as complementary to each other. The anxiety and memory in rodents can be estimated by elevated plus maze test [159]. In passive avoidance test, the animal teaches to stay away from a place or situation in which shock was experienced in the past. Consequently, both tests can measure animals' capability to remember crucial environmental information [160]. In rats treated with curcumin, the improvement in both tests shows towards superior acquisition and retention of memory, and further increased capacity to learn [91]. Therefore, in rats treated with curcumin and the above mentioned AEDs, curcumin inhibited the progression of cognitive deterioration [91, 99]. Since curcumin administration in healthy rats was not associated with any changes in cognitive functions, it shows that curcumin alone does not improve memory in normal rats [91, 157].

Co-administration with curcumin in rat models of cognitive deterioration induced by PB and CBZ compared to controls shows a significant elevation and reduction in the brain reduced GSH and MDA levels, respectively. These could be at least partially responsible for the decrease of PB- and CBZ-induced cognitive deterioration [91].

The influence of curcumin on cognitive functions was further studied in rat PTZ-kindling induced seizure model [161, 162]. Curcumin group compared to controls showed a significant increase in retention latencies in the passive avoidance paradigm and a significant decrease in retention transfer latencies in the elevated plus maze test [161, 162]. Moreover, curcumin pre-treatment improved cognitive functions in PTZ-kindled rats that is at least partially a consequence of observed curcumin anti-seizure activity [157].

Curcumin antiepileptic actions have already been observed in former studies in which curcumin reduced aluminium chloride-induced, PHT-induced, and lead-induced memory deficit in rats [96]. Moreover, it was shown that curcumin raise the cellular GSH levels through promotion of glutamate cysteine ligase genes transcription [195].

Since the administration of curcumin in rats has been shown to be effective in preventing chemical induced seizures, oxidative damage and cognitive deterioration, it may have some potential as a possible neuroprotective agent. Therefore, curcumin could be used as an add-on therapy resulting in improved seizure control and cognitive functions.

Epigallocatechin (EGCG)

Pre-treatment with EGCG in PTZ-kindled rats has been shown to decrease the time of mean seizure phase and increase the duration of the latent period before myoclonic jerks and generalized tonic-clonic seizures occurred in a dose dependent manner compared to PTZ group. Furthermore, EGCG pre-treated group showed marked decrease in MDA and increased in GSH levels in brain tissue, caused by PTZ-induced seizures, compared to controls [196]. In addition, EGCG pre-treatment in lead-induced seizure models has been connected to significant decrease in MDA levels as well as an increase in GSH levels and SOD activity [197]. This is supported by the study where EGCG prevented iron-induced seizures [198].

On the other hand, pre-treatment with EGCG was further shown to significantly improve the declined learning and memory loss. These findings were confirmed by significantly improved results of passive avoidance paradigm and elevated plus maze tests in comparison to the PTZ group. While EGCG alone showed no effects on cognitive functions, this could confirm that EGCG attenuates the impaired cognition induced by PTZ. These observed neuro-protective effects of EGCG on cognitive decline induced by seizures can be at least partially a consequence of its anticonvulsant activity [196].

Therefore, it is suggested that pre-treatment with EGCG might decrease oxidative stress and improve cognitive decline after PTZ-induced seizures [196, 197, 199].

N-acetylcysteine - thiol Containing Compounds

The compounds in the thiol-containing group are similar to the major endogenous antioxidant glutathione. Their antioxidant activity comes from the reducing activity of the thiol group. This sulfhydryl provides an electron to ROS, causing ROS reduction and therefore decreased reactivity. N-acetylcysteine (NAC) is a simplified mimetic of GSH with a similar antioxidant mechanism utilizing the thiol group to reduce ROS [69].

NAC has demonstrated an ability to suppress epilepto-genesis in PTZ model, probably due to the direct antioxidant effect and increase in cellular GSH levels [69, 200].

Resveratrol

Resveratrol is a conjugated aromatic compound with a conjugated bridge between two aromatic rings. The antioxidant activity is due to the ability to delocalize an unpaired electron over an extended conjugated framework, thus stabilizing the radical [113]. Resveratrol was associated with reductions in severity of KA-induced seizures [114].

α-Tocopherol (Vitamin E)

α-Tocopherol is considered to be the main antioxidant substance in the human body, interfering with oxygen and the production of hydroxyl radical in cell membranes, thereby reducing lipid peroxidation [90]. Vitamin E type molecules are highly lipophilic. α -Tocopherol has been reported to prevent neurotoxicity and neurological symptoms in rat models of chemically-induced epilepsy [124]. Convulsive behaviour was attenuated in pentylenetetrazol-, methyl-malonate- and pilocarpine-induced seizures, where brain lipid peroxidation and nitrite content were lowered, while CAT and SOD activities were increased, with resulting

Table 2. Observed anticonvulsive and neuroprotective actions of exogenous antioxidants.

Substance	Cells/Animals/Humans	Seizure Model	References
Potential Antioxidant Actions			
Ascorbic acid (vitamin C)			
Ameliorates convulsive behaviour and neuronal death	Animal model (rats)	PIL/KA/PTZ	[89, 153, 163, 164]
Inhibits initial oxidative stress & maintains GSH homeostasis	Animal model (rats)	Trimethylin	[165]
Directly scavenges free radicals & restores the endogenous antioxidant system	Animal model (rats)	Stress	[166]
Enhances CAT activity and decreased LPO	Animal model (rats)	PIL	[89, 153]
β-catechin			
Oral administration inhibits TBARS formation and increases the activity of SOD	Animal model (rats)	Iron	[167]
Pre-treatment results in a reduction in free radical formation	Animal model (rats)	Iron	[168]
Curcumin			
Neuroprotective effects produced by:			
• maintenance of GSH levels • inhibition of lipid peroxidation	Animal model mice/Astrocytes	KA/-	[92, 169]
• increase of heme oxygenase-1 expression	Animal model (rats)	KA	[168]
Curcumin manganese complex			
Possesses more powerful anticonvulsive and neuroprotective properties	Animal model (rats)	KA	[95, 170]
Animal models show it: • mimic SOD activity • exerts the activity of NO scavenging • suppress markers indicating neuronal injuries	Animal model (rats)	KA	[95, 170]
Ginkgo biloba			
Suppresses seizure generation and seizure induced ROS formation • EGb 761 treated mice display attenuated response to PTZ • pre-treatment protects against PTZ-induced convulsive behaviours • neuroprotection correlates with antioxidant effects	Animal model (mice)	PTZ	[171]
*Neurotoxin (4'-O-methoxypridoxine) exerts pro-epileptic effects	Patients with epilepsy/Healthy subjects	/	[172]
Ginsenosides			
Attenuate seizure activity			
• block KA induced mitochondrial dysfunction and impaired mitochondrial antioxidant capacity	Animal model (rats)	KA	[173]
• attenuate ultrastructural mitochondrial damage & mitochondrial oxidative stress	Animal model (rats)	PIL	[173]
• inhibit synaptosomal oxidative stress & presynaptic ultrastructural damage *via* adenosine A 2A receptor activation	Animal model (rats)	PTZ	[174]
• inhibit NMDA-mediated epileptic discharge	Animal model (rats)	PTZ	[174]
Honeybee propolis			
Pre-treatment significantly attenuates oxidative stress, seizure activity and neuronal degenerations • maintains GSH homeostasis • maintains adenosine A1 receptor activation	Animal model (rats)	KA	[175]

Table 2. contd….

Substance	Cells/Animals/Humans	Seizure Model	References
Potential Antioxidant Actions			
N-acetyl cysteine			
Anticonvulsive actions • markedly improves myoclonus • decreases occurrence of generalized seizure • gradually increases serum GSH levels	Animal model (rats)	Trimethylin/ KA	[165, 176]
Protects against seizures	Animal models (mice)	PTZ	[101]
Omega-3 fatty acids (PUFAs)			
Exert channel modulation, and anti-inflammatory action			
• DHA suppress epileptic seizures and synaptic transmission by blocking hippocampal frequency-dependent Na^+ channels	Animal model (rats)	PIL	[103, 104, 177]
• through inhibition of voltage-gated Ca^{2+} and Na^+ channels, DHA enhance neuronal membrane stability	Animal model (rats/mice)	KA	[171, 174]
Observed anti-convulsive actions in animal studies			
• suppress seizures and delay the latency to seizure onset	Mice/rats	PTZ	[105, 178]
• delay the latency to seizure onset	Mice/rats	PTZ	[106, 107, 179]
• no changes in the latency to seizure onset	Animal model (rats)	PTZ	[180, 181]
• suppress electrographic seizures	Animal model (mice)	KA	[108]
• reduce the frequency of severe seizures	Animal model (rats)	KA/GI	[182]
Anticonvulsant effects of n-3 PUFAs (EPA & DHA) in clinical studies [109]			
• reduce seizure frequency by >50%	Patients with epilepsy	CE	[110]
• transiently reduce seizure frequency	Patients with epilepsy	Int./Ref.	[111, 183]
Plasma concentrations are elevated in children treated with KD	Children with epilepsy	KD	[184]
Resveratrol			
Exerts anticonvulsive and neuroprotective properties, decreases LPO Delays the onset of seizures and decreases LPO	Animal model (mice/rats) Animal model (rats)	KA/AOMS Iron	[171, 185] [186]
α-Tocopherol(vitamin E)			
Pre-treatment with α-tocopherol: • decreases the percentage of animals with seizures, increases time needed to trigger the first seizure, increases survival, decreases LPO and nitrite content, increases SOD and CAT activity	Animal model (rats)	PIL	[122, 125]
Prevents the development of epileptic seizures induced by iron administration	Animal model (rats)	Iron	[135, 187, 188]
Significantly delays the appearance of seizures triggered by intracerebral $FeCl_3$ administration	Animal model (rats)	Iron	[135, 187, 188]
Decreases seizure activity and LPO	Animal model (rats)	Iron	[189, 190]
Improvement in patients with complex partial seizures	Patients with epilepsy	-	[191]
Exerts anticonvulsive and neuroprotective effects - reduced BBB disruption	Animal model (rats)	PTZ	[192-194]
Fails to attenuate seizure activity	Animal model (rats)	KA/Amig. kindl./BIC	[115, 191] [191, 189]

AOMS - artery occlusion model of stroke, CE – chronic epilepsy, DHA - docosahexaenoic acid, EPA - eicosapentaenoic acid, GI – global ischemia, GSH – glutathione, Int. – Intractable, KA – kainic acid, KD – ketogenic diet, LPO- lipid peroxidation, NMDA - N-methyl-D-aspartate, PIL – pilocarpin, PTZ – pentylenetetrazol, PUFA - polyunsaturated fatty acid, Ref. – refractory, SOD - superoxide dismutase, * Ginkgo biloba extracts can contain neurotoxin (4'-O-methoxypridoxine) which can exert pro-epileptic effects.

lower hippocampal damage and increased survival [90, 125, 201]. In animals treated with α-tocopherol plus pilocarpine, the intensity of histopathological changes and mortality rate were lower in comparison to pilocarpine alone [90].

Diverse experimental models show that preliminary injections of α -tocopherol reduce seizure induced oxygen and nitrogen free radicals generation on a time scale of minutes-to-hours [124]. Short-term dietary α -tocopherol supplementation reduces brain lipid peroxidation even four days after KA-induced seizures. Together with a high consumption rate of brain α -tocopherol observed in supplemented rats after seizures, this finding indicates that conditions of oxidative stress initiated by SE persist long after the earliest post-ictal phases and that α-tocopherol can play a prolonged antioxidant effect after the triggering event. α-Tocopherol markedly reduces neuronal cell death after SE [124].

There is also considerable evidence of the prophylactic and inhibitory effects of α-tocopherol on the development of iron-induced epileptic seizures. α -Tocopherol has been shown to importantly delay the onset of epileptic seizures triggered by intra cerebral $FeCl_3$ administration [135].

6.2.3. Novel Synthetic, Potent Antioxidants

α-Tocopheryl-L-ascorbate-2-O-phosphatediester

α-Tocopheryl-L-ascorbate-2-O-phosphatediester (EPC-K1) represents a potent synthetic scavenger of hydroxyl radicals. EPC-K1 has been demonstrated to inhibit the formation of

Table 3. Observed anticonvulsive and neuroprotective actions of novel, potent antioxidants.

Substance	Cells/Animals/Humans	Model	References
Potential antioxidant actions			
Aspalatone			
GPx mimetic [202]			
• inhibits seizures, oxidative stress, and hippocampal neuronal death	Animal model	KA	[115]
• enhances antiperoxidative enzyme activity, like GPx and CAT in blood			
• directly scavenges hydroxyl radicals, but not SOD	*In vitro* ESR study	-	[115]
EUK-134 (new, potent SOD mimetic)			
Prevents oxidative stress and reduces neuronal damage [117]			
• blocks neuronal death, LPO, nitrite formation and NA oxidation	*In vitro* model	-	[203]
• mediates suppression of:	Animal model	KA	[127]
o AP-1 and NF-jB DNA-binding activity			
o transcription factors susceptible for oxidative stress			
• does not affect seizure latency and duration	Animal model	KA	[117, 118]
MnTBAP			
Inhibits mitochondrial oxidative stress and neuronal loss • inhibits rat hippocampal superoxide production, 8-OHdG formation and neuronal loss • inhibits neuronal loss in hippocampus CA3 region by 60% • prevents KA-induced mitochondrial aconitase inactivation by 75% • inhibits KA-induced raise in 8-OHdG/2-dG ratio by 50% • inhibits mitochondrial O2- formation and DNA oxidative damage with no effects exerted on behavioural seizures	Animal model (rats)	KA	[118-120]
Tempol			
Protects neuronal cells and exerts anticonvulsant effects via: • suppression of apoptosis • suppression of SOD formation • inhibition of nitrite formation	Animal models	KA	[121]
There were no effects exerted on seizure-like activity in hippocampus	Animal models	KA	[121]

8-OHdG – 8-hydroxy-2-deoxyguanosine, AP-1 – activator protein, CAT – catalase, DNA – deoxyribonucleic acid, ESR - electron spin resonance, GPx – glutathione peroxidase, GSH – glutathione, MnTBAP – Mn(III)tetrakis (4-benzoic acid) porphyrin, KA – kainic acid, LPO- lipid peroxidation, NF – nuclear factor, SOD - superoxide dismutase

thiobarbituric acid reactive substances (TBARS) and protein carbonyl (P-Carb), induced by ferric ions *in vitro* in a dose dependant manner. Furthermore, pre-treatment or simultaneous treatment with EPC-K1 suppresses or delays the appearance of epileptic seizures induced by ferric ions [116].

As seen above, ROS have been implicated in seizure-induced neurodegeneration. These findings support the appropriateness of introducing the addition of antioxidants as an add-on to classical AEDs treatment. Most of the studies performed so far have confirmed that antioxidants as an add-on therapy could potentially, at least to some extent, provide neuroprotective effects against seizure-induced neurotoxicity (Tables **1**, **2**, and **3**).

7. STUDIES OF ANTIOXIDANTS USAGE IN VARIOUS ANIMAL MODELS OF EPILEPSY

Numerous studies in animal models of seizures and epilepsy have been conducted in order to evolve the influence of an add-on antioxidant treatment on enzymatic antioxidant activity (SOD, CAT, GPx and GR), non-enzymatic endogenous antioxidant status (GSH), ROS markers (hydroperoxide), various markers of macromolecular oxidative stress damage (MDA, TBARS, 8-OHdG, mtDNA damage and P-carb), and nitrate/nitrite levels. Practically all antioxidants, including endogenously present α-lipoic acid [70, 73, 143, 204], coenzyme Q_{10} [87] and melatonin [135, 142, 145, 147, 148], exogenous anticonvulsive and neuro-protective substances, such as ascorbic acid [66, 89, 135, 153, 164, 165], curcumin [96, 99, 100, 205, 206], ginsenoside-Rd [207-209], propolis [175], α-tocopherol [122, 125, 135, 193, 201, 210], and naringin [211], and novel synthetic, potent radical scavengers, like aspalatone [115], EPC-K1 [135], and tempol [121], have shown neuroprotective effects against oxidative stress induced by different proconvulsive substances that are usually used in models of seizures and epilepsy, as summarized in the Table **4**.

The majority of studies have confirmed neuroprotective effects of antioxidants, showing increased levels of endogenous antioxidant enzyme activities, increased endogenous non-enzymatic antioxidant levels, namely GSH and decreased markers of macromolecular oxidative stress damage in comparison to untreated animal models of seizures and epilepsy. However, there were few exceptions. Curcumin in seizure induced rats showed a decrease in CAT [100, 212] and GSH [100] levels and exerted no effect on MDA levels [205]. Ginsenoside-Rd in aging senescence-accelerated mouse (SAM) showed no effects on SOD and CAT activities [207]. Furthermore, tempol in KA-induced rats exerted decreased SOD activities [121]. A summary of findings from these studies is given in Table **4**.

Oxidative stress occurring in the brain throughout substance-provoked seizures has been shown to play an important role in pathogenic consequences of seizures. As seen in Table **4** investigated potent antioxidants in animal models exert strong antioxidant effects. These findings therefore greatly support the idea of important neuro-protective and hence possible anticonvulsive role of using appropriate potent antioxidants as an add-on therapy in epilepsy.

8. STUDIES OF ANTIOXIDANTS USAGE IN PATIENTS WITH EPILEPSY

Based on the abundance of observed beneficial effects of antioxidants on markers of oxidative stress *in vitro* and *in vivo* in animal models of epileptic seizure, various antioxidants, namely vitamin E, melatonin and NAC, have also been used in patients with epilepsy as an add-on therapy [81, 83, 102, 104, 213-216]. On the other hand, unfortunately there is a lack of quality data obtained from straight clinical studies of antioxidants use in patients with epilepsy, and furthermore even the existing results are confusing.

For instance, Ogunmekan *et al.* reported that α-tocopherol as an add-on significantly reduced seizures in children [214], while Raju *et al*. observed no significant difference between α-tocopherol and placebo in adults [213]. Ogunmekan *et al.* published a randomized, double-blind, placebo-controlled clinical study in 24 children with medically refractory epilepsy. He investigated the effect of α-tocopherol supplementation on seizure control. It was noticed that the addition of D-α-tocopheryl acetate in a dosage of 400 mg/day produced a significant decrease in seizure occurrence in ten of twelve patients with epilepsy. Controls showed no changes in seizure incidence. Furthermore, since there were no changes in the plasma anticonvulsants concentrations, clinical benefits were attributed to increased serum E vitamin levels [214]. On the other hand, another randomized, double-blind, placebo-controlled clinical trial, evaluating the effect of the addition of D-α-tocopherol to the conventional AEDs treatment, carried out in 43 adults with refractory epilepsy, did not support the possible therapeutic effect of vitamin E [213].

Besides these two newer studies, there are also two older studies published which have evaluated the efficacy of α-tocopherol treatment in epilepsy. Kovalenko *et al*. have observed beneficial effects already one month after the α-tocopherol administration (600 mg once daily) in patients with confirmed pharmacoresistant epilepsy. Decreased lipid peroxidation, positive EEG alteration and reduced frequency of epileptic seizures were reported in the majority of patients [217]. Similarly, Tupeev *et al.* investigated the effect of 600 mg of α-tocopherol applied daily as an add-on to conventional AEDs therapy. Only after one month of additional therapy, they reported greatly improved patients' general state, achieved namely through decreased epileptic seizure frequency, which was further supported by an observed increase in SOD activity and consequently significant improvement in EEG results. They concluded that using of α-tocopherol in the multiple-therapy approach to epilepsy treatment improved neuroprotective and antiepileptic effects [218].

Currently, only a few studies of using melatonin as add-on therapy in patients with epilepsy have shown potential beneficial effects on decreased epileptic seizures incidence. Assessing the effects of melatonin on the blood levels of antioxidant enzyme GPx and GR in children with epilepsy receiving CBZ monotherapy compared to the placebo group, showed significantly and non-significantly increased

Table 4. Effects of potential antioxidants on oxidative stress markers in different animal models of seizures and epilepsy.

Antioxidant	Animal	Seizure Model	Observed Marker	Results	Investigated Material	References
α-Lipoic acid	Rats	Aging	SOD, CAT, GPx and GR	↑	Cortex, cerebellum, hippocampus, striatum and hypothalamus	[204]
			MDA	↓		
	Rats	PIL	SOD and CAT	↑	Striatum	[70]
			GPx	↑	Striatum/Hippocampus	[70, 143]
			MDA and NO	↓	Striatum	[70]
			GSH	↑	Hippocampus	[143]
			Na^+ and K^+ ATP-ase	↑	Hippocampus	[143]
	Rats	PIL	SOD, CAT and GPx	↑	Striatum/Hippocampus	[70, 73]
			MDA and NO	↓	Striatum/Hippocampus	[70, 73]
α-Tocopherol	Rats	PIL	SOD	↑	Hippocampus/Striatum	[125, 210]
			CAT	↑	Hippocampus/Striatum	[125, 210]
			LPO and nitrite	↓	Hippocampus/Striatum	[125, 210]
	Rats	PTZ-kindled	TBARS and P-Carb	↓	Striatum	[201]
			LPO	↓	Whole brain	[193]
	Rats	PIL	CAT	↑	Hippocampus	[122]
	Rats	Iron injection	H_2O_2	↓	Whole Brain	[135]
Ascorbic acid	Rats	PIL	SOD	↑	Hippocampus	[66]
			CAT	↑	Hippocampus	[66, 89, 153]
			MDA	↓	Hippocampus	[66, 89, 153]
			NO	↓	Hippocampus	[66]
	Rats	PTZ-kindled	P-carb	↓	Striatum	[164]
			Na^+ and K^+ ATP-ase	↑	Striatum	[164]
	Rats	TMT	MDA	↓	Hippocampus	[165]
			P-carb and GSSG	↓	Hippocampus	[165]
			GSH	↑	Hippocampus	[165]
Aspalatone	Rats	KA	P-carb	↓	Whole brain	[115]
			MDA	↓	Whole brain	[115]
Curcumin	Rats	PTZ-kindled	GSH	↑	Whole brain	[96]
			MDA	↓	Whole brain	[96]
	Mice	PTZ-kindled	GSH	↑	Whole brain	[206]
			MDA	↓	Whole brain	[206]
	Rats	PTZ-kindled	CAT	↓	Cerebrum, Cerebellum	[100]
			GSH and MDA	↓	Cerebrum, Cerebellum	[100]
	Rats	PIL	NOS and LDH	↓	Hippocampus	[205]
			SOD and GSH	↑	Hippocampus	[205]
			MDA	-	Hippocampus	[205]
	Rats	PIL	CAT, MDA and NO	↓	Hippocampus	[212]
			GSH and Na^+ and K^+ ATP-ase	↑	Hippocampus	[212]
	Rats	Phenytoin	GSH	↑	Whole brain	[99]
			MDA	↓	Whole brain	[99]

Table 4. contd….

Antioxidant	Animal	Seizure Model	Observed Marker	Results	Investigated Material	References
EPC-K_1	Rats	Iron injection	MDA	↓	Whole brain	[135]
			P-carb	↓	Whole brain	[135]
Ginsenoside-Rd	Mice-SAM	Aging	SOD and CAT	-	Liver, serum	[207]
			GPx and GR	↑	Liver, serum	[207]
			MDA	↓	Liver, serum	[207]
			GSH and GSH/GSSG	↑	Liver, serum	[207]
			GSSG	↓	Liver, serum	[207]
	Rats	Focal cerebral ischemia injury	SOD, CAT and GR	↑	Cerebral artery	[208]
			GSH/GSSG	↑	Cerebral artery	[208]
			8-OHdG, P-Carb, AGE, MDA	↓	Cerebral artery	[208]
	Mice	Aging	SOD and GPx	↑	Serum	[209]
			MDA	↓	Serum	[209]
Melatonin	Mice	KA induced	mtDNA damage	↓	Whole brain	[145]
			MDA	↓	Whole brain	[145]
	Rats	KA induced	MDA	↓	Brain synaptosomes	[142]
			ROS generation	↓	Brain synaptosomes	[142]
	Rats	KA induced	GPx and GR	↑	Forebrain	[148]
			GSH	↑	Hippocampus, amygdala	[148]
	Rats	KA induced	GSH, GSH/GSSG	↑	Striatum and cortex	[149]
	Rats	Iron injection	GPx	↑	Whole brain	[135]
		Iron injection	NO formation	↓	Whole brain	[135]
	Rats	Iron induced	TBARS	↓	Cortex	[147]
Naringin	Rats	KA induced	GSH	↑	Whole brain	[211]
			MDA	↓	Whole brain	[211]
Propolis	Rats	KA induced	MDA and P-carb	↓	Hippocampus	[175]
			GSH/GSSG	↑	Hippocampus	[175]
Tempol	Rats	KA induced	SOD and DNA fragm.	↓	Hippocampus	[121]
Ubiquinone	Rats	PIL	SOD, CAT and GPx	↑	Hippocampus	[87]
			H_2O_2	↓	Hippocampus	[87]

↓ - decreased, ↑ - increased, - no significant changes observed, 8-OHdG - 8-hydroxydeoxyguanosine, AGE - advanced glycation end-product, CAT – catalase, DNA – deoxyribonucleic acid, GPx - glutathione peroxidase, GR – glutathione reductase, GSH – glutathione, GSSG - glutathione disulfide, H_2O_2 – hydrogen peroxide, KA – kainic acid, LDH - lactate dehydrogenase, mtDNA – mitochondrial DNA, MDA – malondialdehyde, NO – nitric oxide, NOS - nitric oxide synthase, PIL – pilocarpin, PTZ – pentylenetetrazol, ROS – reactive oxygen species, SAM - senescence-accelerated mouse, SOD – superoxide dismutase, TBARS - thiobarbituric acid reactive substances, TMT –trimethylin

GR and GPx activities, respectively [83]. Similar findings were found in a study in children with epilepsy on VPA monotherapy [81]. Both of these studies demonstrate that melatonin exerts neuroprotective effects due to its antioxidant and antiexcitotoxic properties within the central nervous system [81, 83].

In a small clinical study of six children with intractable seizures, the addition of melatonin to the conventional AED treatment, demonstrated an improvement in seizure control in five cases. Moreover, after discontinuation of melatonin, all six patients have claimed their seizure activity returned to pre-treatment levels [84].

Another clinical study, performed in children with epilepsy investigated the effect of melatonin administration to the conventional AEDs on patient's life quality. Since there were noticed an improvement in physical, cognitive and social functions, emotional well-being, and behaviour, it is suggested that melatonin may have beneficial neuro-protective effects when used as an add-on therapy in patients with epilepsy [82].

There is also a published study of using melatonin in children with sleep disturbances and therapy-resistant epilepsy. Six of ten participated children with epilepsy showed a significant decrease in epileptic seizure frequency, which could be a consequence of anticonvulsant effects as well as reduced sleep deprivation, caused by melatonin [85].

Moreover, in a patient with Unverricht-Lundborg disease, the influence of NAC treatment on serum GSH concentrations was studied. GSH concentrations increased during treatment, which corresponded to improved seizure control with exception in myoclonus and ataxia. There were also patients who showed a variable response [216]. Ben-Menachem *et al*. reported significantly reduced myoclonus and further decreased incidence of generalized seizures in numerous case reports of using NAC [215].

It is important to keep in mind that in patients with non-refractory epilepsy, even better responses to antioxidant as add-on therapy, could be expected. After all, for more reliable conclusions of potential beneficial effects of antioxidants, more carefully planned, randomized, double-blind, cross-over, placebo-controlled clinical trials including appropriate number of patients and a longer duration of oxidative stress biomarkers monitoring, are needed. Furthermore, to the best of our knowledge, till now no clinical studies have been performed, which would investigate the potential benefits of many other known antioxidants, such as ascorbate, flavonoids, melatonin, lipoic acid, exogenous novel potent mimetics of catalase or SOD, and coenzyme Q_{10}, in the case of epilepsy in humans. Moreover, at this time even the assessment of beneficial effects of antioxidants as add-on treatment in the field of common genetic and acquired epilepsies can be considered as incomplete. Therefore, on the basis of the published studies and reports, it is very difficult to provide any relevant final conclusions of the potential benefits of using antioxidants as add-on neuroprotective therapy. To prevent potentially misleading conclusions, novel carefully designed and more comprehensive studies are needed.

9. POTENTIAL LIMITATIONS OF USING ANTI-OXIDANTS AS ADD-ON THERAPY IN EPILEPSY

The use of dietary supplements is very popular among the people around the world and patients with epilepsy are no exception. Despite the lack of evidence of their beneficial effects in epilepsy, studies confirmed that dietary supplements are consumed by 10 to 56% of patients with epilepsy [219-223]. Among reported dietary supplements many antioxidants can be found [219, 221]. In generally patients consider dietary supplements as safe medications with no adverse side effects. Although this is confirmed in some reports from clinical trials or case reports investigating dietary supplements use in patients with epilepsy, some studies also report that dietary supplements can affect central nervous system and potentially increase the risk of seizures [172, 219, 224, 225]. Moreover, the concomitant treatment of AEDs and dietary supplement can change effects of AEDs, since AEDs are highly prone to drug-drug and drug-dietary supplement interactions. The potential interactions between antioxidants and AEDs can be explained by pharmacokinetic (changes in absorption, distribution, metabolism or elimination) or pharmacodynamic (changes in drug effects or efficacy) mechanisms. The two most probable pharmacokinetic mechanisms by which antioxidants can interact with AEDs are *via* cytochrome P450 enzymes and transporter proteins. Ginkgo biloba induces CYP2C19 and can reduce the levels of phenytoin and valproate which are both substrates for this enzyme [172, 226]. Data about the effect of vitamin E on CYP are less evident. According to some reports Vitamin E may induce CYP3A4 [227, 228] and thus can reduce levels of carbamazepine, ethosuximide, felbamate, phenytoin phenobarbital, tiagabine, and zonisamide, which are all substrate for this enzyme [229]. Moreover, it was shown that resveratrol can inhibit CYP3A4 and increase levels of carbamazepine in rats [230]. We can also speculate that this interaction would probably occur with above mentioned AEDs which are substrates for CYP3A4. Resveratrol is also inhibitor of multidrug resistance-associated protein 2. This mechanism can also contribute to increased levels of CBZ in combination with resveratrol [230]. Additionally, AEDs are also substrates of P-glycoproteins and concomitant treatment with curcumin, catechins, and ginkgo biloba can probably affect their levels [172]. Therefore, concurrent use of antioxidants with AEDs, can lead to an increase or decrease in AED plasma concentrations. This can potentially results in an increase or decrease of drug efficacy, an increase of drug toxicity or in an increase in its adverse side effects. However, the potential clinical implication of interactions between concurrent use of antioxidants and AEDs is difficult to predict and assess. For this reason it is important to stress out that antioxidants should not be used concurrently with other drugs without proper medical supervision.

10. CONCLUSION

Oxidative stress has been revealed as one of the most important processes leading to neuronal cell death. Therefore, it is rational to anticipate that oxidative stress has a considerable role in epileptogenesis. There is an accumulation of free radicals and oxidative changes expressed during the acute phase after the initial insult or SE induced by various triggers and the latent phase in experimental models of epilepsy. This finding suggests that seizures, SE and cell death induced by different triggers, might possess a large participation in brain oxidative stress, which is closely related to the mechanism of propagation and/or maintenance of the epileptic focus. Furthermore, there is an accumulation of evidence that in patients with epilepsy the balance of antioxidant system is disturbed, and the production of free reactive radicals is increased.

Neuronal cells death resulting in neuronal loss appears to represent one of the most important neurobiological alterations in the epileptogenic and epileptic brain. Therefore, the use of antioxidants as add-on therapy should lead to less sever structural damages, reduced epileptogenesis and milder cognitive deterioration. Most of the conventional AEDs do not prevent neuronal damage resulting from prolonged or multiple seizures. Therefore, there is a strong need to develop newer antiepileptic treatments, including novel AEDs with broad spectrum of actions or conventional AEDs in combination with potent antioxidants, which would pose simultaneously neuroprotective and antiepileptogenic effects. The former effects seem to be very important,

especially in the latent period, where targeted therapies could potentially prevent the progression of epileptic seizures, namely through epileptogenesis inhibition.

Only recently, the perception of epilepsy has extended from a condition almost entirely related to neurons to a condition further associated with the dysfunctions of glial cells. Astrocytes, representing the largest subgroup of glial cells, are known to play a crucial role in regulating and maintaining the extracellular chemical milieu of the central nervous system. Additionally, they interact with neurons, modulate neurons synaptic transmission, and participate in inflammation processes. It is therefore reasonable to propose a potentially important role of glial cells in epileptogenesis, as was indicated in few studies [231]. Moreover, we speculate that oxidative stress can also modulate the function of glial cells which can contributes to progression of epileptogenesis. However, new studies are needed to confirm this hypothesis.

In order to evaluate potentially positive effects of therapeutic interventions with antioxidant components, numerous studies of their use in animal models of epileptic seizures, were revised. However, even though numerous positive effects of antioxidants were observed in animal models of epileptic seizure, till now only few antioxidants have been further evaluated in patients with epilepsy as an add-on therapy and even these with only partial success. Based on the several positive findings in animal models, a strong need for more carefully planned, randomized, double-blind, cross-over, placebo-controlled clinical trials for the evaluation of antioxidants efficacy in patients with epilepsy is warranted.

Currently, upon enhanced investigation of possible causes and consequently improved understanding of underlying mechanisms of epileptogenesis, many new possibilities for epilepsy therapy have revealed. Future is currently reflected in designing newer AEDs, which will include anticonvulsant and neuroprotective activity. Therefore, it is of great importance to closely monitor various potent antioxidant systems and to study the possibilities of their inclusion to conventional AEDs treatment, which according to some studies can lead to improved life quality in patients with epilepsy.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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LIST OF ABBREVIATIONS

8-OHdG	=	8-hydroxy-2-deoxyguanosine
ADP	=	Adenosine diphosphate
AEDs	=	Antiepileptic drugs
AGE	=	Advanced glycation end-product
AOMS	=	Artery occlusion model of stroke
AP-1	=	Activator protein
BBB	=	Blood brain barrier
CAT	=	Catalase
CBZ	=	Carbamazepine
CE	=	Chronic epilepsy
CI	=	Confidence interval
CNS	=	Central nervous system
DHA	=	Docosahexaenoic acid
DNA	=	Deoxyribonucleic acid
EEG	=	Electroencephalogram
EGCG	=	Epigallocatechin
EPA	=	Eicosapentaenoic acid
EPC-K1	=	α-Tocopheryl-L-ascorbate-2-O-phosphate diester
ESR	=	Electron spin resonance
GABA	=	γ-aminobutyricacid
GI	=	Global ishemia
GPx	=	Glutathione peroxidase
GR	=	Glutathione reductase
GSH	=	Glutathione
GSSG	=	Glutathione disuphide
H2O2	=	Hydrogen peroxide
Hb	=	Haemoglobin
Hb ASSG	=	Glutathione adduct of haemoglobin
KA	=	Kainic acid
KD	=	Ketogenic diet
LA	=	Lipoic acid
LDH	=	Lactate dehydrogenase
LPO	=	Lipid peroxidation
MDA	=	Malondyaldehyde
MnTBAP	=	Mn(III)tetrakis (4-benzoic acid) porphyrin
mtDNA	=	Mitochondrial DNA
NAC	=	N-acetlcysteine
NF	=	Nuclear factor
NMDA	=	N-methyl-D-aspartate
NO	=	Nitric oxide
NOS	=	Nitric oxide synthase
PB	=	Phenobarbitone
P-Carb	=	Protein carbonyl

PHT	=	Phenitoin
PIL	=	Pilocarpin
PTZ	=	Pentylenetetrazol
PUFA	=	Polyunsaturated fatty acid
RNA	=	Ribonucleic acid
RNS	=	Reactive nitrogen species
ROS	=	Reactive oxygen species
RR	=	Relative risk
SAM	=	Senescence-accelerated mouse
SE	=	Status epilepticus
SOD	=	Superoxide dismutase
TBARS	=	Thiobarbituric acid reactive substances
TMT	=	Trimethylin
VPA	=	Valproic acid
WMD	=	Weighted mean difference

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