[Frontiers In Bioscience, Elite, 9, 214-234, March 1, 2017]

Potential of redox therapies in neurodegenerative disorders

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1. ABSTRACT

Recently significant advances have been made to understand the pathophysiological mechanisms of neurodegenerative disorders to provide real therapeutic benefits. There is evidence that persistent inflammation and oxidative stress are the crucial factors of ongoing cell damage in neurodegenerative complex etiology. The variety of reactive oxygen and nitrogen species are the cause of both axonal and neuronal destruction, which is pathological hallmark of neurodegeneration. Therefore, the reduction of oxidative stress is currently one of the main neuroprotective strategies. The World Health Organization (WHO) estimates that, by 2040, neurodegenerative diseases will be the main cause of death in industrialized countries ahead of the cancers. The redox therapeutic approch can target: degnerative component, inflammatory/autoimmune component and neurodegenerative component. Redox therapy should not be applied uniformly, and must be develop to target specific mechanisms. This review focus on the main antitoxidative therapies that are used in many countries as a supplements or even as a standart treatment. Aditionally, clinical synmptoms of most

common neurodegenerative disordes and central nervous system structures involved in oxidative/ nitrosative stress are showed.

2. INTRODUCTION

Neurodegeneration is the hallmark of aging processes characterized by progressive dysfunction of nervous system with specific clinical, morphological and biochemical features. They include Alzheimer's Disease (AD) and other dementias, Parkinson's Disease (PD), Multiple Sclerosis (MS), Amyotrophic Lateral Sclerosis (ALS) and less common such as, Huntington's Disease, Prion Diseases, and others. The main clinical symptoms of neurodegeneration are cognitive, motor, and/or behavioral impairment connected with atrophy of central and/or peripheral structures of the nervous system. The World Health Organization (WHO) estimates that, by 2040, neurodegenerative diseases will be the main cause of death in industrialized countries ahead of the cancers (1).

Therefore, the neuroprotective compounds and therapies in prevention and treatment are very needed. Accumulating data showed that there are many similarities mainly on molecular level in different neurodegenerative diseases. Discovering these links might be the main point for new therapeutic strategies. This parallels concern not only oxidative stress but also other typical features of neurodegeneration such as persistent inflammation, atypical protein assemblies and apoptosis. Although no effective treatments are yet available, current studies are focused not only on symptomatic treatment but also on prevention mainly by cytoprotective mechanisms described in this review. The growing body of evidence indicates a leading role of oxidative stress as a cause of nurodegeneration on a molecular level. Oxidative damage may affect not only DNA but also the major proteins of key cellular processes. The redox therapeutic approch can target: degnerative component, inflammatory/autoimmune component and neurodegenerative component. Redox therapy should not be applied uniformly, and must be develop to target specific mechanisms.

The progression of age-dependent neurodegeneration is associated with decreased antioxidants and increased oxidative damage to proteins, DNA and lipids. Oxidative protein modification occurs at a low and persistent level in diverse cells and tissues, and accumulates with aging. This review shows evidence of oxidative/nitrosative injury in main neurodegenerative diseases, discuss effects and challenges of redox therapies both in animal and clinical trials. To achieve this goal, a better understanding of cellular targets and processes involved in neurodegeneration and regeneration is needed. Thus, in this review, we discuss the various redox therapies used in the management of neurodegenerative diseases, namely AD, PD, MS, Glaucoma, ALS and HD (2).

3. CNS STRUCTURES INVOLVED IN OXIDATIVE/NITROSATIVE STRESS

Normal CNS ageing is characterized by variety of biochemical changes, such as increased oxidative stress, persistent microinflammation and altered energy metabolism (reviewed in Prolla and Mattson 2001 (3)). Futhermore, ageing tends to cause metabolic changes by mechanisms shared with neurodegenerative disorders, such as excitotoxic damage and increased calcium ion influx, leading to cell death by necrosis and apoptosis. Aging is connected also with brain atrophy, enlargement of the ventricles, a decreased activity of enzyme, including NaATPase and higher membrane permeability. The brain regions most affected by atrophy are the hippocampus and frontal lobes (4). Moreover, brain ageing is also associated with significant changes in phospholipid fatty acid composition. In physiological conditions neurons have low capacity for cellular regeneration. Therefore, neurodegeneration results is irreversible and gradual progresses causing clinical symptoms such as motor and/or mental functioning (dementias). Moreover, neurons are highly vulnerable to oxidative/ nitrosative stress due to their terminally differentiated morphology, metabolic and antioxidative dependence on surrounding astrocytes and glia. They are also very active and highly susceptible for oxygen and glucose reduction.

Astrocytes are multifunctional cells that constitute about 90% of CNS. They participating in metabolism, neuroprotection, neuroplasticity, neurotransmission and regulation of blood flow. The early stages of neurogeneration are associated with the activation of common inflammatory pathways, involving microglia and astrocytes activation, and the release of pro-inflammatory cytokines and other inflammatory mediators that regulate astrocytic hypertrophy and proliferation (5). Persistent inflammation leads to reactive astrogliosis and increased expression of various genes, including glial fibrillary acidic protein (GFAP), a component of astrocytic filaments and commonly utilized marker of reactive astrogliosis.

Neural damage results in astrogliosis and upregulation of GFAP in response astrocytes proliferate, migrate, and form glial scars that protect surrounding neuronal tissue from further damage. Reactive astrocytes can also produce several factors (cytokines, chemokines and neurotrophic factors) affecting brain injury (6). Microglia are characterized by different type of glial cell. They are the macrophage-derived resident immune cell that are maintain homeostasis in CNS microenvironment and activate in response of any changes. In physiological conditions, microglia mon-

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itoring synaptic pruning, ultimately affecting neuronal connectivity and signaling.

The blood - brain barrier (BBB) and blood-cerebrospinal fluid barrier (BCSFB) are the key structures in brain homeostasis. In neurodegenerative disorders, entrance of immune cells through the brain barriers is facilitated (7). The BBB is a selective physical barrier that composed from capillaries surrounded by perivascular macrophages and astrocytic endfeet. In this way astrocytes can directly modulate BBB function and regulate blood transport between the circulation and CNS parenchyma. Capillaries in CNS are in tight junctions that provide diffusion of small gaseous molecules such as NO_2, O_2 and CO_2 and some lipophilic compounds but strictly reduce the entrance of large hydrophilic molecules including proteins. Neuronal membrane lipids are rich in polyunsaturated fatty acids (PUFA) side chains. PUFAs composed of eicosapentanoic (C20:5) and decosahexanoic (C22:6) acids are particularly vulnerable to free radical attack because of the double bonds, within the membrane allowing easy removal of hydrogen ions by ROS such as OH (8).

Antioxidant defense in CNS is rather low. Catalase (CAT) activity is significantly decreased in all brain regions. Furthermore, CNS contains less glutathione peroxidase (GPx), and vitamin E as compared to liver. However, the concentration of ascorbic acid, which can act as an antioxidant is elevated in both white and gray matter. Reports have showed that GSH is the major cellular antioxidant against ROS induced adverse effects, and its activity is closely related to cell survival. GSH is synthesized from glutamate, cysteine and glycine. Cysteine is the rate-limiting precursor of GSH synthesis. Neurons are considered to contain less glutathione than astroglial cells. *In vitro* studies have showed that in neuronal culture the GSH concentration range from 1-40 nmol/mg protein (9-11). Extracellular concentration of glutamate in CNS is normally low <μM. Several ROS are able to decrease glutamate uptake by glial cells and to inactivate glutamine synthetase, preventing conversion of glutamate to glutamine. This enzyme is inactivated in Alzheimer's disease. The early drop in cellular glutathione (GSH) levels observed together with oxidative glutamate toxicity is very similar to the changes seen *in vivo* within neurons responding to both acute and chronic injury.

4. OXIDATIVE/NITROSATIVE STRESS

Oxidative/nitrosative stress is strongly implicated in neurodegeneration patophysiology and might provide a critical link between environmental factors such as heavy metals, viral infections, herbicides and genetic risk factors. However, a number of controversies begin to emerge in this field. It is suggested that, from one point of view, oxidative stress is an epiphenomenon of damaged and dying neurons, but, from another, oxidative stress itself is the cause the of gradually damage leads to death of neurons. Mitochondria are the key organelles due to the fact that in the CNS 4x 10^{12} ATP/minute is necessary to maintain neuronal intracellular ion homeostasis. Moreover, mitochondria are not only main ATP producer, but also a significant source of intracellular oxidants $-H_2O_2$ and $^{\cdot}NO$. Longitudinal studies participants between 19–85 ages show a lower redox status as indicated by the linear oxidation of cysteine/cystine (Cys-SH/CysS-S) and GSH/GSSG (only after 45 years). This linear prooxidant shift indicates a chronic increase in oxidative events in lifespan.

5. NRF2-ARE PATHWAY

According function antioxidative proteins can be divided into 2 groups: the ROS-detoxifying enzymes, including superoxide dismutases (SODs), glutathione peroxidases (GPXs), and catalase. These enzymes in normal state are expressed in all cells by transcriptional regulation, that is the effect of function the other group of antioxidant proteins, transcription factors (TFs) such as peroxisome proliferator–activated receptor γ coactivator 1-α (PGC1a) and nuclear factor erythroid–derived 2, like 2 (NRF2, also known as NFE2L2). PGC1a and NRF2 are the main TFs that regulate whole antioxidant system. PGC1a is a pleiotropic transcriptional coactivator. Cell regulates its endogenous antioxidant capacity is through activation of NRF2. Regulation occurs by binding to the antioxidant response element (ARE) in their regulatory regions. The ARE element is a cis-acting regulatory element that governs the expression of phase II detoxification enzymes. Expression of several detoxifying, cytoprotective, and antiinflammatory genes is boosted by NRF2. NRF2 acts via an "on-demand" mechanism. KEAP1 suppress this mechanism under physiological conditions, with nuclear accumulation upon stimulation by oxidation (12). Both groups of antioxidant genes have been proposed as therapeutic candidates, e.g., for neurodegenerative disorders NRF2 promotes neuronal survival in neurodegeneration and acute nerve damage (13).

A multitude of genes involved in redox status, anti-inflammation and detoxification are transcribed by Nrf2-ARE pathway activation. These genes are known to be involved in cytoprotection from various oxidative insult and cellular injuries in numerous different tissues and organs including brain. Antioxidant enzyme systems regulated by Nrf2 include, but not limited to, redox regulation (superoxide dismutase (SOD), catalase (CAT), sulfaredoxin (Srx), thioredoxin (Trx), peroxiredoxin (Prdx) system), glutathione synthesis and metabolism (glutathione peroxidase (Gpx), glutathione reductase (GR), γ-glutamine cysteine ligase (GCL) and synthase (GCS)), quinone recycling (NAD(P)H quinone oxidoreducase (Nqo1)) and iron homeosta-

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sis (heme oxygenase 1 (HO-1), Ferritin). Some antioxidant genes have more active roles than others in brain depending on the disease condition, cellular environment or cell type (12 14). In CNS, the Nrf2-ARE dependent gene expression is preferentially less activated in neurons compared to astrocytes (15 16). Recently research is focused at either astrocytic Nrf2 overexpression-mediated protection of neurons or modulating endogenous neuronal antioxidant capacity by small molecule Nrf2 activators or cell specific overexpression. Several disease specific studies involving Nrf2 activation/overexpression as a therapeutic strategy showed its ability to modulate the progression of major neurodegenerative disorders. Supplementary to its primary role in cytoprotection, Nrf2 is also linked to differentiation, proliferation, growth, apoptosis and it is thought that Nrf2 has evolved from an original role in haematopoiesis and the regulation of cell differentiation from early lineages (17).

6. NITRIC OXIDE AND PEROXYNITRITE

Nitric oxide (NO) has a very important role in the CNS. It can be produced by all brain cells including endothelial cells, neurons, glial cells (astrocytes, oligodendrocytes and microglia) by calmodulin Ca^{2+}/calmodulin dependent NOS-isoforms. In physiology NOS in neurons (nNOS) and endothelial cells (eNOS) produce very low amount of NO (nanomolar) in response to transient higher level of intracellular Ca^{2+}. NO is pleiotropic molecule responsible not only for cerebral blood flow but also for neuronal transmission, synaptic plasticity, modulation of neuroendocrine functions, memory formation and cognitive function. The production of NO is induced by excitatory stimuli amplifying toxicity in the CNS. Even slight induction of expression of iNOS in CNS cells results large amount of NO. NO can form RNS such as peroxynitrite, in combination with some forms of oxygen such as superoxide. Nitric oxide may take part in nitrosylation of proteins; however, peroxynitrite is a highly reactive nitrogen species that can nitrate tyrosine residues of proteins and change their function. Peroxynitrite formation has been implicated in AD, PD, HD, MS, ALS pathophysiology. Nitrotyrosine immunoreactivity has been found in early stages of all of these diseases in human autopsy samples as well as experimental animal models. Increased nitrite, nitrate and free nitrotyrosine has been found to be present in the cerebral spinal fluid (CSF) and proposed to be useful marker of neurodegeneration. Once formed peroxynitrite in CNS may exert its toxic effects by several mechanisms including lipid peroxidation, mitochondrial damage, protein nitration and oxidation, depletion of antioxidant reserves (especially glutathione), activation and inhibition many signaling pathways and DNA damage followed by the activation of nuclear enzyme PARP. Postmortem tissues from patients with AD, PD, HD, ALS or FA show oxidative damage in the affected brain regions (18).

7. CARBONYL STRESS

Advanced Glycated End Products (AGEs) are markers of carbonyl stress. Its accumulation is connected with increased level of sugars and reactive dicarbonyl compounds (19). AGEs are formed as a consequence of oxidative stress and in turn induce oxidative stress, amplifying damage in the CNS (20). AGE formation is irreversible process due to protease-resistant cross-linking of peptides and proteins, leading to protein deposition and amyloidosis. AGEs are the cause of cell damage by various mechanisms including direct neurotoxicity involving oxidative stress and apoptosis. Methylglyoxal (MG) has been suggested to be the main source of intracellular reactive carbonyl compounds involved in neurodegeneration (19).

8. REDOX THERAPIES IN NEURODEGENERATION

8.1. Ginkgo biloba

Ginko biloba is used *in vitro*/vivo studies as EGb761 (standardized extract of the leaves of the *G. biloba* tree) characterized by its main fractions, the flavonols glycosides 22–27%, terpene lactones (5–7%) and less than 5ppm ginkgolic acids. EGb761 is one of the commonly used herbal therapies for dementia and cognitive impairment. Potential neuroprotective properties of EGb761 were observed on molecular level (reduction of amyloid-β (Aβ) aggregation and Aβ toxicity). This polyvalent radical scavenger have the ability to optimized mitochondrial function as well as improve microperfusion. Moreover, this multitasking drug has very good safety and tolerance level. Several *in vitro* studies on rats models showed that EGb761 might strengthen neurotransmission especially glutamatergic (21), dopaminergic, and cholinergic systems. The systematic review and metaanalysis by Tan *et al.* show that in patients (n=2561) with dementia and cognitive impairment from 9 trials (placebo-controlled trials of 22–26 weeks duration) benefits from EGb761 therapy for stabilizing or slowing decline in cognition, function, behavior and clinical changes but this effects are mainly reached in the dose 240mg/day dose (21 22).

Results Yang *et al.* also suggest that Ginkgo might be effective as additional therapy in AD patients with cognitive impairment but without impact on its progression (23). However, the efficacy of *G. biloba* in AD is not clear. A 6 months regulatory trial carried out to obtain FDA marketing approval for EGb761 did not show efficacy for mild-to moderate AD. Furthermore, the Ginkgo Evaluation of memory trial demonstrated that *G. biloba* does not prevent dementia in elderly individuals with or without memory complaints or cognitive impairment and is not effective for prevention of AD (24). Few clinical trials have tried to examine the effectiveness of *G. biloba* in preventive AD. Among

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these preventive trials is Guid Age - a multi-centre, randomized, double-blind, placebo-controlled, parallel-group, 5 year study- conducted in 13 subgroups in France. The research has aimed to assess the efficacy of long term daily administration of 240 mg of a standardised *G. biloba* extract in lowering the risk of AD. The study was unsuccessful in showing the protective effects of *G. biloba* for the incidence of AD (25). Finally, in a meta-analysis review, the authors concluded that despite promising results, broad recommendations for the use of *G. biloba* in neuropsychiatric conditions, such as AD are still premature (26 27).

8.2. Coenzyme Q_{10}

Coenzyme Q10 (2,3-dimethoxy-5-methyl-6-decaprenil-1,4-benzoquinone) is a liposoluble compound also known as CoQ_{10}, vitamin Q_{10}, ubidecarenone or ubiquinone. It is obtained from the diet prodacts or supplements, but is also produced endogenously about 3-5 mg per day in the mitochondria. The highest concentration of Co Q_{10} in human tissues is at the age of twenty years, then gradually decreases. Co Q_{10} is not classified as a vitamin or mineral, so it is no dietary reference value is recommended. CoQ10 is one of the main cofactors involved in mitochondrial oxidative phosphorylation and also act as antioxidant (28 29). *In vitro* studies show that Co Q_{10} easily crosses the BBB. The phase III trial of CoQ10 in PD, QE3, is currently enrolling, and will shed some light on the question of a therapeutic range, with doses of 1,200 mg versus 2,400 mg of CoQ_{10} (30). CoQ10 levels are significantly decreased in mitochondria from SN neurons and platelets in PD patients, and levels of Co Q_{10} have been shown to correlate with activity of complexes I and II/III (31). The nervous system is exposed to oxidative stress, and this may emphasize the role of Co Q_{10} in the CNS especially in oxidative phosphorylation, metabolism of neurons with the constant and high energy demand of these cells. The property of CoQ_{10} to be potent both as a pro-oxidant and an antioxidant suggests possible role as a modulator of cellular redox state in age related diseases. The mitochondrial inner membrane contains CoQ_{10} and α-tocopherol demonstrated that Co Q_{10} protects the cells from apoptosis, not only morphologically but also on molecular level (32). The first clinical studies concerning neuroprotective effects of Co Q_{10} was reported in 1994 by Beal *et al.* This study showed that the intake of 1200 mg per day of Co Q_{10} for sixteen months was associated with 44% less functional decline in PD patients (33). Another study in twenty-eight patients with PD also showed moderate improvement in symptoms with daily oral administration of 360 mg of CoQ_{10} (34). It has been shown that CoQ_{10} improves cognitive functions, regulates mitochondrial functions and facilitates the synthesis of ATP (35).

Coenzyme Q_{10} is promising antioxidant especially in PD studies. In-vitro studies using fibroblasts from PD patients showed that exogenously administered CoQ_{10} restore electron transport chain activity. As a lipophilic antioxidant, CoQ_{10} is capable of scavenging radicals within membranes and in the cytosol and plasma when bound to lipoproteins. Preliminary data from a phase I study suggested that that exogenously administered CoQ_{10} may retard disease progression in PD. Platelet CoQ_{10} redox ratios have been shown to be significantly decreased in PD patients (36). CoQ_{10} supplementation also resulted in decreased serum levels of MMP-9 as compared to the placebo group. However, CoQ_{10} supplementation did not change the IL-4 and TGF-β levels. CoQ_{10} supplementation at a dosage of 500 mg appears to decrease the inflammatory markers (TNF-α, IL-6, and MMP-9) in the group of 24 MS patients. The intervention was administered for 12 weeks (37).

8.3. Selenium

Selenium is an essential micronutrient with very narrow recommended dietary range. The RDA for selenium is approximately 55 lg/day and selenium can be obtained from suplemennts and dietary intake. Selenium, in the form of selenocysteine, is a constituent of 25 classes of selenoproteins, including GPxs, selenoproteins P, W, and R, and thioredoxins(TrxR). Moreover, selenium, could act as immunomodulator, antioxidant and anti-inflammatory factor. Approximately 60% of selenium in plasma is present as selenoprotein P (38 39) This protein differs from other selenoproteins in that it incorporates up to 10 Se atoms per molecule in the form of selenocysteine as opposed to the single selenocysteine incorporated in other selenoproteins. Most studies are found the role in Alzheimer's and cognitive impairment (40-42).

Another study in France evaluated selenium levels in 1389 elderly patients (60–71 years) over time and found that short-term decline in selenium levels had no effect on cognitive function but longitudal, selenium deficiency may contribute to reduced neurological cognitive function. Additionally, Aguilar *et al.* have reviewed the role of selenium in multiple sclerosis, Alzheimer's and Parkinson's disease (43). Changes in selenium concentration in diseased brains with Alzheimer's disease and multiple sclerosis were reported, but no change in selenium levels were observed in studies with Parkinson's disease (44-48).

Selenoprotein P levels can be maintained in the CNS independent of plasma selenium level (38). However, genetic ablation of selenoprotein P results in reduced, but it is compensate by other selenoproteins and supporting the hypothesis that basal selenium levels are essential for the brain and have a priority. Reduced dietary selenium can have significant effects on levels of selenoproteins involved in oxidative stress, such as glutathione peroxidases, thioredoxin reduc-

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Table 1. The potential of nutraceuticals and pharmacotherapies with redox activity in neurodegenerative disorders

Pharmaceuticals	Standardized extract (compound)	Dosage	Therapeutic strategy	BBB	Disorder	Function and role *In vitro**/vivo	Ref.
Ginko biloba	EGb761	240-360 mg/day	Cognition Memory Attention		Alzheimer's Disease	reduce amyloid (Aβ) aggregation and Aβ toxicity an inhibitor of the platelet activating factor (PAF) receptor*	[1,2,3]
Ubidecarenone	Coenzyme Q10	produced endogenously 3–5 mg per day 30-200mg per day	Cognition	+	Parkinson disease Multiple sclerosis	protects the cells from apoptosis; decrease the inflammatory markers (TNF-α, IL-6, and MMP-9)	[4] [5]
Selenium	Selenoproteins glutathione peroxidase (GPx), thioredoxin reductase (TrxR), and selenoprotein P (SeP).	55 micrograms (mcg)/day	selenium deficiency may contribute to reduced neurological cognitive function		Alzheimer's disease Parkinson Disease Multiple sclerosis	Seleno-L-methionine protects against amyloid (Aβ)and iron/ hydrogen peroxide-mediated neuron death*; Protection of hippocampal neurons *	[6] [5]
Curcumin	Tumeric	Standardized powder (curcumin): 400 - 600 mg, 3 times per day Fluid extract (1:1) 30 - 90 drops a day Tincture (1:2): 15 - 30 drops, 4 times per day	Cognition	+	Alzheimer's disease Parkinson Disease	reduce amyloid (Aβ) levels and plaque burden* detoxification of ROS and peroxynitrite; Increase GSH synthesis*; suppresses the activation of transcription factor NF-kB*	[20]
Cannabinoids	Dronabinol (2.5mg delta-9-tetrahydrocannabinol (delta-9-THC) Nabilone CBD (cannabidiol) Nabiximols Ratio of 2.7mg Δ9-THC, 2.5 mg	2.5-20mg/day 100 mg (0.03mg/kg) 65-120mg/day	Cognition Memory Sympathomimetic activity; Tremor and spasticity; Dystonia and dyskinesia Neuropathic pain		Parkinson Disease Alzheimer's disease ALS Multiple sclerosis	Antioxidant activity; Decreases proinflammatory cytokines (TNF-α, IL-1β), and NFkB activity; protected dopaminergic ncurons• Increase trophic factors and anti-inflammatory cytokines (IL-10). Prevents excitotoxicity by reducing glutamate release and signaling; Promotes oligodendrocytes survival, reducing demyelination and apoptosis	[9-13] [16,17] [12]
Melatonin	N-acetyl-5-methoxytryptamine	0.1-20mg/day	Quality of sleep Cognition	+	Multiple sclerosis Alzheimer's disease	Increase of SOD, GPx and decrease of MDA in erythrocytes; increased hippocampal synaptic density and the number of excitatory synapses, decrease the number of inhibitory synapses, and upregulated pre- and postsynaptic proteins	[15] [16,18,19]
Omega-3 fatty acid	EPA (Eicosapentaenoic acid) DHA. (docosahexaenoic acid)	250-4000 mg/day EPA/DHA 1 g contains 180 mg (EPA) / 120 mg (DHA).	Cognition		Alzheimer's disease	decreases NaTPase activity, increase the levels of hippocampal BDNF*	[13,14]

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tases and methionine sulfoxide reductases. Selenium, through the incorporation into selenoproteins, provides protection from reactive oxygen species (ROS)-induced cell damage and neuroplsticity. Selenoprotein P deficiency results in subtle spatial learning deficits and severe synaptic plasticity defects. It is difficult to discern whether this is due to selenoprotein P itself, or the loss of selenium transport to the CNS (49). Exposures to high levels of environmental selenium have been associated with motor neuron disease in both animals and humans and high levels of selenite have been identified in the cerebrospinal fluid of patients with amyotrophic lateral sclerosis (ALS).

8.4. Curcumin

Curcumin (diferuloylmethane) is a component of turmeric, natural plant polyphenol derived from the spice. It is widely used as a food flavoring and coloring agent (e.g., in curry). Curcumin was demonstrated to exert pleiotropic cellular effects, which include antioxidant activity and direct detoxification of ROS and peroxynitrite as well as prevent toxicity associated with pathological protein aggregation (50). Hence, the neuroprotective efficacy of curcumin has been assessed in various diseases of mitochondrial metal dysfunction including AD, PD and stroke models. Moreover, curcumin is able to cross the BBB. Treatment of astrocytes with curcumin induced the cytoprotective proteins HO-1, NQO1, and GST and provided protection against the damaging effects of glucose oxidase-mediated toxicity. Further, curcumin was reported to bind to amyloid plaques, and to reduce amyloid levels and plaque burden in aged (51 52). Its rapid elimination from the brain has resulted in several drug design approaches to improve bioavailability. Curcumin and its derivatives have been tested in numerous cell and animal models of PD. Treatment of N27 dopaminergic neurons with a glutamic acid substituted curcumin derivative-induced neuroprotection involving increased GSH synthesis and a reduction in oxidative stress, lipid peroxidation and H_2O_2 production (53). N27 neurons were also protected from MPP+-induced cytotoxicity by Di-glutamoyl curcumin (54). Furthermore, curcumin improved survival of dopaminergic neurons in the SN in MPTP-lesioned C57BL/6 mice via JNK-dependent inhibition of mitochondrial swelling and cytochrome c release (55). Curcumin-fed rats that had been 6-OHDA- lessoned displayed elevated striatal dopamine levels and had a decreased number of iron-positive cells in the SN, suggesting that curcumin-mediated iron chelation may be responsible for protection of dopaminergic neurons from Fenton chemistry-dependent neurodegeneration (56 57). Curcumin has also been reported to reduce Huntington accumulation and improve rearing behaviour in HD CAG140 knock-in mice (58). Similar to CuII(atsm), the cellular mechanism of action of curcumin involves activation of kinase signalling pathways. Pharmacological inhibition of the Akt, but not MAPK, path- ways decreased curcumin-stimulated Nrf2 activation and Nrf2-dependent gene expression in primary rat cultured cortical neurons (59), including both the PD-associated α-synuclein and ALS-associated TDP-43 (60-63).

8.5. Omega-3 fatty acid

Omega-3 fatty acid (Docosahexaenoic Acid) have been shown to influence a number of membrane proteins, such as receptors, ion channels and enzymes. Futhermore, they can also modulate dopaminergic, serotoninergic, cholinergic neurotransmission and regulate signal transduction pathways. Chronic omega-3 PUFA deficiency significantly decreases NaTPase activity in rat brain (64). DHA is the most complex form of Omega-3 and is difficult to include in our diet as only few foods contain a significant amount. Other forms of Omega-3 are inefficiently converted to DHA in our body. Omega-3 DHA is taken up directly into cell membranes, whereas plant-derived fatty acids are not. Fats account for over 50% of the brain and Omega-3 DHA represents 30% of brain matter. The highest concentration of Omega-3 DHA in the human body is in the retina where it helps to reduce inflammation which is almost unavoidable event in most of the neurodegenerative diseases.

With aging and in AD patients the level of DHA is significantly lower in blood plasma and brain (65). This not only could be due to lower dietary intake of omega-3 fatty acids, but it also could be connected with increased oxidation of PUFA (66).

Dietary supplementation of DHA has been shown to increase the levels of hippocampal BDNF (67). Calon and colleagues (68) found that a diet rich in DHA activates Ca^{2+}/calmodulin-dependent protein kinase (CaMKII). This signalling cascade is critical for learning and memory and plays a crucial role in induction and maintenance of long-term potentiation in hippocampus. In summary, results from controlled studies conducted over the last 10 years suggest that nutritional intervention with omega-3 fatty acids is beneficial only in the earlier stages of cognitive impairment.

AD is strongly correlated with lower level of omega-3 PUFA both in brain and peripheral tissues. Decreased DHA content in serum phosphatidylcholine has been suggested as a significant risk factor for developing AD.

8.6. Melatonin (MLT)

MLT is well known as a potent neuroprotectant and effective antioxidant. MLT is able to pass easily through the blood brain barrier and enters into all cells with its lipophilic and hydrophilic nature. MLT production gradually decline with the aging and numerous studies have associated this decrease with

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highier induction of oxidative stress and age-associated degenerative changes. Melatonin increases enzymatic antioxidative defensive systems, including SOD and GPx as well as the levels of glutathione and the decreased pro-oxidant enzymes activity, especially 5- and 12-lipo-oxygenase and nitric oxide (NO) synthases. The majority of endogenous melatonin is directly released from the pineal gland to the cerebrospinal fluid (CSF). Up to 20 folds lower fraction is released into the capillary blood where it is distributed to all tissues. Additionally, recent studies showed that melatonin has potential to effectively bind and inactivate endogenous iron. Thus it can suppress the Fenton reaction and in the consequence decrease overproduction of ROS (33). Receptor-independent effects of melatonin are based on its direct binding to calmodulin, thus causing inhibition of Ca^{2+}/calmodulin-dependent kinase II (49) and Ca^{2+}-dependent membrane translocation of protein kinase C (50). Melatonin can also prevent specifically the activation of the pro-inflammatory enzymes COX-2 and iNOS in glioma cells, thus indicating an anti-inflammatory action. Importantly, melatonin does not alter COX-1 protein level.

To determine the action of MLT in the reduction of oxidative stress in MS, lipid peroxidation and activities of main antioxidative enzymes in the red blood cells (RBCs) from group of MS patients with secondary progressive clinical course were studied. The patients were supplemented with MLT (10 mg daily/30 days). MLT caused statistically significant increase of SOD, GPx and decrease of MDA in erythrocytes of MS patients. The results showed that use of MLT in MS patients could be taken into account, especially in progressive form of MS (69). Last studies report that addition of 30 mol% MLT to the anionic membranes significantly reduced the membrane-embedded Aβ state (70).

8.7. Cannabinoid

The cannabinoid system presents a promising target for the treatment neurodegenerative disorders. CB1 and CB2 are two major cannabinoid receptors. Those receptors have been cloned and several endogenous cannabinoids were identified along with their synthetic and degradative pathways. ECBs are located not only in the brain, but also in the periphery in humans and animals. ECBs are produced by cultured neurons, microglia and astrocytes. Low levels CB1 receptors have found on mitochondrial membrane suggesting a direct relationship between CB1 receptor and mitochondrial functions in the brain. The phenolic ring moieties in cannabinoids display antioxidant activity and guard against glutamate-induced neurotoxicity in a cellular model. (71).

The cannabis resin and flowers was isolated in 1964 as Δ^9-tetrahydrocannabinol (Δ^9-THC). Since that time, numerous non-psychoactive cannabinoids have been identified, such as cannabidiol (CBD), cannabigerol (CBG), cannabichromene (CBC), Δ^9-tetrahydrocannabivarin (Δ^9-THCV) and cannabidivarin (CBDV). The most widely studied phytocannabinoid is Δ^9-THC. Sativex® is used to alleviate spasticity in adult multiple sclerosis (MS) patients which haven't respond to other drugs during an initial trial period of therapy. Several side effects associated with cannabinoid administration were observed: euphoria, somnolence, and tiredness, but these did not warrant discontinuation of therapy. Cannabinoids might represent low-cost and safe therapy. Currently, the endocannabinoid system is a novel therapy for AD patients. due to it potent neuroprotective, anti-inflammatory, and neurotrophic properties. The synthetic phytocannabinoid, HU- 211, has been shown to act as a stereoselective inhibitor of N-methyl-D-aspartate (NMDA) receptors and thereby protect rat forebrain cultures and cortical neuronal cultures from excitotoxicity (72-74). Cannabinoids can also modulate the brain-derived neurotrophic factor (BDNF) to amplify neuroprotection against excitotoxicity (75). In a mouse model of AD, which received an intrahippocampal administration of Aβ1-42, CBD prevented reactive gliosis and the release of proinflammatory mediators (76). CBD has also been shown to dampen Aβ-induced GSK-3β activation thereby preventing tau hyperphosphorylation and the subsequent formation of neurofibrillary tangles (77).

8.8. Vitamin E and C

Vitamin E and C Prevention of neuronal death can be also achieved by functional foods performing neuroprotective effects through antioxidant actions. A higher intake of vegetables, fruits, and seeds rich in vitamin C, carotenoids and vitamin E is positively associated with better cognitive function and a decreased risk of dementia in the elderly. The reduction the prevalence of AD in aged people can be associated with the combination of vitamin E and vitamin C intake (78 79).

9. OTHER REDOX THERAPIES

9.1. Physical Exercise

Existing hypotheses suggest that physical exercise represents a potential adjunctive treatment for cognitive impairment. This may help to delay the onset of neurodegenerative processes. Exercise appears to stimulate neurogenesis, enhance neuronal survival, increase resistance to brain insults and increase synaptic plasticity. In individuals 65 years and older, physical activity has been shown to protect against the continuous development of AD. In addition, regular moderate physical exercise can positively influence depressive symptoms in AD patients (80 81). In the Canadian Study of Health and Aging, individuals aged 65 years or older who were engaged in regular physical activities had a 50% reduced risk of developing AD (82 83).

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10. NEURODEGENERATIVE DISORDERS AND REDOX THERAPIES

10.1. Parkinson disease

Parkinson's disease (PD) is the second most common neurodegenerative disorder after Alzheimer's disease characterized by progressive and massive loss of dopaminergic neurons in the midbrain, which leads to several motor symptoms. PD occurs worldwide, with equal incidence in both males and females. The prevalence increases exponentially with age between 65 and 90 years. The mean age of onset is about 65 years. However, 5-10% of people who develop PD, experience symptoms before the age of 40 (young onset). Motor symptoms of PD involve bradykinesia, rigidity, tremor and postural instability. PD patients also suffer from non-motor symptoms such as disturbances of olfaction, vision, sleep and of the autonomic nervous system. Moreover many PD patients present neuropsychiatric symptoms such as anxiety, fatigue, apathy, anhedonia, depression and dementia. Symptoms of PD start to appear when 50-60% of SNc dopaminergic neurons and 70-80% of striatal nerve terminals are lost. Research data have clearly indicated that during PD, SN dopaminergic neurons are subject to oxidative and nitrosative stress, and mitochondrial dysfunction, proteasome inhibition and protein aggregation. In PD ROS contributes to BBB dysfunction. Moreover, metalloproteinase-9 (MMP-9) activity, involved in degrading the basal lamina was increased by oxidative stress, whilst antioxidant treatment of brain ECs prevented MMP-9-induced TJ disassembly (84).

Moreover, brains from PD patients show evidence of elevated oxidative damage to DNA (85), lipid peroxidation and oxidative modification of proteins (86), decreased levels of reduced glutathione (GSH) and increased monoamineoxidase (MAO) activity(87 88), that indicate reduced antioxidant defense mechanisms. Dopamine oxidation by MAO leads to the formation of ROS (87) and, if not effectively detoxified by glutathione, hydrogen peroxide might potentially induce the generation of highly reactive hydroxyl radicals in the presence of excess iron via the Fenton reaction. Lewy bodies, considered cytopathologic markers of parkinsonism, comprise abnormal arrangements of tubulin and microtubule-associated proteins, MAP1 and MAP2. Melatonin effectively promotes cytoskeletal rearrangements and was assumed to have a potential therapeutic value in the treatment of parkinsonism, and, perhaps, generally in dementias with Lewy bodies (89 90).

Drug treatment provides symptomatic relief, reduce disability, maintain independent functioning and thus improving quality of life of the patient. Currently firs line standard treatment includes L-dopa, dopaminergic agonists, monoamine oxidase B inhibitors and drug combinations. Other medications include catechol-O-methyltransferase, anticholinergic agents and amantadine (91 92). Evidence suggests that elements of the cannabinoid system may play a neuroprotective role in PD via inhibition of oxidative and inflammatory processes.

10.2. Alzheimer Disease

The development of Alzheimer's disease (AD) is closely connected with deposition of amyloid beta plaques (AB) and neurofibrillary tangles in tissue brain (93). There are more evidence that one of the main cause of AD is closely associated with aggregation these specific protein for neurodegenerative diseases especially in the neocortex which is affiliated with pathological interactions metal ions such as Zn, Cu as well as Fe in this area of humans' brain (94). During the aging process tissue brain accumulates the metal ions, but the presence of antioxidants are responsible for providing the oxidative homeostasis. However alterations in oxidative metabolism, which are one of the hallmark in AD, indicate that oxidative stress play the crucial role in AD pathogenesis (95).

AB is derived from amyloid β protein precursor (APP) during the cleavage of the APP by enzyme BACE1 (96 97). APP molecules include metal binding domain for cooper and zinc, which are located in the N-terminal region and are similar to the family of proteins known as cooper chaperons whose main hallmark is affinity for reducing ions Cu^{2+} *in vitro*. The zinc binding domain is described as the structural domain, but the vital role of cooper binding provides the ability to reduce molecule of Cu^{2+} to Cu^{+} and moreover promotes neurotoxicity of cooper as well as disturb the metal homeostasis in neuronal cells. The conducted research indicate that APP knockout mice was characterized by increasing levels of Cu, and mice with overexpression of APP were characterized by decreasing levels of Cu mainly in the brain cortex. Decreased APP may contribute to increase the level of cooper which as a result leads to AB aggregation and moreover releasing the free radical forms of AB. Imbalance in cooper homeostasis in humans' brain could lead to initiation and progression the AD, since the cortex is the area of brain primarily affected in the AD (95 98 99).

Furthermore, AB plaques might also bind metal ions *in vitro* which plays the vital role in increasing its levels in the neocortex and leads to significant accumulation of AB molecules among the neurons in brains of individuals with AD, for instance zinc ions markedly increase precipitation of AB plaques (100). It has been also reported that AB plaques may reduce Cu^{2+} to Cu^{+} which generates the H_2O_2 in neurons cell and moreover it is associated with neurotoxicity of AB plaques caused by Cu^{2+} ions(101).

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Recent investigations based on metal imbalance in tissue AD brain present a new point of view on therapeutic strategy for AD. The potential therapeutic target in AD are chelating agents which has the potential to prevent and what is the most important reverse AB deposition in the AD brains. However, one of the problems for this approach was connected with chelators bioavailability and its toxicity, but recent research indicate that for instance covalent conjugation iron chelators with nanoparticle may facilitate their transport by blood-brain-barrier and reduce their toxicity (102 103). Moreover, conjugated nanoparticles with chelators not altering their ability to bind metals. The novel therapy based on deliver chelators to the AB plaques in AD brains and transport the complex metal-chalators from the brain tissue which may play the crucial role during the prevention of inducing the reactive oxygen species by AB which results in neuronal loss during the progression of AD (102 104).

The key neuropathological hallmarks of AD include deposition of amyloid beta (Aβ) plaques and the presence of neurofibrillary tangles composed of the hyperphosphorylated form of the microtubule associated protein, tau. Therapeutic approaches to AD are symptomatic relief with low efficacy. Two classes of drugs currently approved for use by the FDA include the acetylcholinesterase inhibitors, namely donepezil, galantamine and rivastigmine and the N-methyl-D-aspartate (NMDA) receptor antagonist memantine. Acetylcholinesterase inhibitors are indicated for patients with mild to moderate symptoms while memantine is recommended for moderate to severe cases of AD. Currently, disease modifying drugs (DMD) are being pursued against amyloid deposition, tau deposition, inflammation and oxidative stress (105). The postmortem histopathological analysis confirmed an elevated lipid peroxidation and DNA oxidation and protein reorganization in the brain cortex in the brains of AD patients with typical changes in cytoskeletal architecture. The antioxidative protection against A-beta of melatonin has been confirmed by Pappolla *et al.*, which showed that co-incubation of both murine neuroblastoma (N2a) and pheochromocytoma (PC12) cells with A-beta-peptides and melatonin greatly reduced the degree of A-beta-induced lipid peroxidation, thus greatly increasing the survival of the cells (102). *In vitro* studies demonstrated that melatonin could protect from neurofilaments hyperphosphorylation changes and accumulation induced by calyculin A (CA), through not only its antioxidant effect but also its direct regulatory effect on the activities of protein kinases and protein phosphatases. The melatonin concentration in CSF is decreased that gradually progresses in AD. Moreover, melatonin levels both in CSF and in postmortem human pineal gland are already reduced in early stage of AD with no cognitive impairment (106-109). Therefore, CSF melatonin level has been suggested as an early marker for the detection of AD. With regard to the anti-inflammatory effects of melatonin, the most important feature is its inhibition of mitochondrial iNOS expression (110 111) Another approach being investigated is targeting the mitochondria which are involved in the pathology of AD. As such MitoQ, an orally active antioxidant currently in development by Antipodean Pharmaceuticals Inc, is now undergoing Phase II clinical trials for the potential treatment of neurodegenerative diseases. MitoQ which comprises of a ubiquinone moiety is believed to be a promising antioxidant candidate for treating AD patients (112).

10.3. Glaucoma

Glaucoma is the second most common cause of blindness in the world (113). The main factor for glaucoma is elevated intraocular pressure (IOP). Treatment consists in reducing the IOP, and this is so far the only available therapy, although it is known that this is not the only factor causing this damage of *retinal gangion cells (RGC) and their axons* resulting in loss of vision. Glaucoma is now recognized like a multifactorial neurodegenerative disorder (114 115). In 1990 Weinreb and Levin suggested that neuroprotection of glaucomatous optic nerve should be an additional therapy to traditional intraocular lowering-pressure treatment (116 117).

The goal of neuroprotective treatment is to reduce or slow damage to RGC (118 119). We have many clinical studies that show the influence of drugs to prevent damage to the RGC. The largest neuroprotection in glaucoma clinical trial investigated the efficacy of memantine an NMDA receptor antagonist *(Irvine, CA, USA; "Memantine in Patients With Chronic Glaucoma", clinicaltrials.gov NCT00168350)*. Despite good results in glaucoma preclinical studies, Phase 3 of the study did not confirm these results. Although memantine can prevent neuronal necrosis but did not affect apoptosis of these cells caused by oxidative stress. Therefore, just as in Alzheimer's disease, attempts to add vitamin D to mematine, which has an antioxidantive and anti-inflammatory effect. For this purpose, new clinical trial started in France (120). Brimonidine tartrate 0.2.% ophthalmic solution (Alphagan, Allergan), a highly selective alpha 2-adrenergic agonist used in the management of ocular hypertension and glaucoma has also neuroprotective effect demonstrated in animal studies (121). However, due to the large number of patients (55%) which was missing in a 4-year follow-up, you can not refer to the results of this clinical trial.

Ginkgo biloba disturbed ocular microcirculation, oxidative stress, impairment of mitochondrial function in the retinal ganglion cells and could have potentially neuroprotective effect in glaucomatous patients. Because of the possibility of complications, such as bleeding, headache, and the fact that there is one clinical trial evaluating its effectiveness in glauco-

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ma, it is not a drug commonly used (122 123). Another antioxidants such α-lipoic acid, 17β-estradiol containing eye drops and estrogens was also shown neuroprotective effects in preclinical studies (124-126). Some clinical trials which tested antioxidants (α-tocopherol, Gingko biloba and an antioxidant formula) was in Phase 3 study but the results are still not know. Calcium channel blockers relieve pressure in eyes and increase blood flow in patients with open-angle glaucoma (127 128). Calcium channel blocker such as Flurizine (129), Nimodipine (130), Nilvadipine (131) and Lomerizine (132) demonstrate neuroprotective effect in many experimental and clinical studies. Secreted protein brain-derived neurotrophic factor (BDNF) have been studied and evaluated in multiple clinical trials. It showed a beneficial neuroprotective effect of retinal ganglion cells, such as: improved survival, protection of RGCs (133 134). In conclusion glaucoma is multifactorial neurodegenerative disorder. Recent clinical trials show that neuroprotection in glaucoma treatment (especially antioxidative theraphy) can be effective and widely used in the future. Despite this, further clinical trials and approved widely available drugs are needed.

10.4. Amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS) is a fatal motor neuron disease, affecting both the first and second motoneuron. The main feature of ALS progression is degeneration of motor neurons associated with massive demyelination in the anterior horn of the spinal cord. The etiology is not entirely understood. There are three major processes suggested in ALS pathophysiology: (a) mutations of the superoxide dismutase 1 (SOD1) gene, causing a toxic gain of function with enhanced reactivity towards abnormal substrates (tyrosine nitration), along with an impaired ability to bind zinc leading to a reduced antioxidant capacity; (b) mutations in neurofilament genes and oxidative modifications or hyperphosphorylation of cytoskeletal proteins leading to selective motor axon degeneration; (c) excitotoxicity caused by increased cerebrospinal fluid glutamate levels together with a loss of excitatory amino acid transporters (170). In SOD1(G93A)-transgenic mice, high-dose oral melatonin delayed disease progression and extended survival. In a clinical safety study, chronic high-dose (300 mg/day) rectal melatonin was well tolerated during an observation period of up to 2 years (135).

10.5. Multiple sclerosis

Multiple sclerosis (MS) is a chronic progressive heterogenous disease of CNS leading to focal plaques of demyelination in both white and grey matter, together with profound axonal and neuronal degeneration (46). is The main reason of disability progression is axonal loss. Recent studies, suggest that oxidative damage is one of the main biochemical process in MS pathogenesis. The number of T cells and macrophages shows statistically significant correlation with the level of oxidation of DNA and lipids (136).

Iron is also discussed as a factor promoting oxidative injury in degenerating oligodendrocytes or myelin during demyelination (137). There are four main clinical types of MS relapsing-remitting (RR), secondary-progressive SP, primary-progressive (PP), and relapsing-progressive (RP). Recent studies pointed out that melatonin genes pathway seems to be involved in MS progression. These data showing the association of polymorphisms in the TPH2 and MTNR1B genes with the progressive subtypes of MS and disability suggest dysregulation in melatonin pathway. Melatonin abolishes destructive cuprizone effects in the corpus callosum by decreasing oxidative stress, restoring mitochondrial respiratory enzyme activity and fusion and fission processes as well as decreasing intra-axonal mitochondria accumulation. Protective effects of melatonin against mitochondrial injury in a mouse model of MS were observed.

Schwarz *et al.* analyzed wide range of complementary and alternative medicine using: diet modification (41%), omega-3 fatty acids (37%), vitamin D (28%), Vitamin E (28%) and vitamin C (28%) homeopathy (26%) and selenium (24%). Majority out of 1573 MS patients (69%) were satisfied with the effects of complementary treatment. Compared with conventional therapy complementary and alternative therapies rarely showed side-effects (9%vs59%) (138).

Currently, very promising results of MS patients are connected with Fumaric acid esters (FAE) therapy used in psoriasis treatment for over 30 years. This drug has been involved in altering response to oxidative stress via nuclear-related factor E2-related factor 2 (Nrf2). The Nrf2 pathway increases expression of antioxidative proteins and in this way provides neuroprotection and homeostasis of immune system.

Moreover, fumaric acid esters are oral therapy what is very rare way of drug application in MS (139 140). The results of randomized, placebo-controlled phase II study indicate significant positive effects of FAE on diverse MRI parameters in MS patients. It has been shown in clinical studies in psoriasis that FAE caused a decrease of peripheral CD4+ and CD8+ T-lymphocytes by stimulation of apoptotic processes (141). Oral dimethyl fumarate (DMF, Tecfidera) was approved for treatment patients with RRMS in 2013. DMF has not only anti-inflammatory but also neuroprotective properties. Neuroprotection is mediated by activation of the nuclear factor (erythroid-derived 2)-related factor 2 (Nrf2) antioxidant pathway. Nrf2 nuclear translocation was shown in neurons, oligodendrocytes, and astrocytes in experimental autoimmune encephalomyelitis (EAE), an animal model of MS, as

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well as in astrocytes *in vitro* after DMF application. Nrf2 is also might induced as a natural response in MS brains, as has been shown in autopsy studies (140). *In vitro* studies showed dimethylfumarate ester's inhibitory effect in human endothelial cells on nuclear factor kappa B (NF-B)-dependent transcription of tumor necrosis factor-alpha (TNF-) induced genes. Experimental studies of EAE demyelinated CNS showed distinct neuroprotection myelin and axons. Molecular reports reports that these processes are dependent on the antioxidative mechanism thorough transcription factor Nrf-2 stimulation. A phase II clinical trial in RRMS patients with dimethylfumarate presented a substantial decrease in the number of gadolinium advancing lesions after 24 weeks (84, 85). This positive immunomodulation seems to be similar to first line of DMD that are basic treatment of RRMS in the early phase. Many years of treatment in psoriasis showed safety profile of dimethylfurmate (DMF) formula BG12. Treatments targeting oxidative injury or protecting mitochondria were shown to be beneficial (142 143).

11. CONCLUSIONS

The therapeutic approaches presented in this review show a large body of promising therapies in treating neurodegenerative diseases. The main benefit from using redox therapies is the protective action on CNS cells function by antioxidant mechanisms that prevent toxic processes. The evidence from both *in vitro/vivo* models reported that ROS/RNS damage occurs in neurodegenerative disease. Redox therapies appear as a very useful way to alleviate typical clinical symptoms including cognitive impairment, spasticity, pain and others. Although, antioxidant therapies has been rather ineffective in clinical trials in slowing down the disease progression. There may be several explanations underlying these findings, including the diverse mechanisms of pro-oxidant action in disease pathology and the advanced nature of the oxidative damage at the time of clinical presentation. However, recently several medications with redox properties has been approved for the treatment CNS disorders including cannabinoids or BG12 (Tecfidera) an oral drug composed of dimethyl fumarate (DMF) that of RRMS. The clinical results suggest that an activation of nuclear translocation of Nrf2 after fumarate is main neuroprotective pathway. The other problems with providing trials are plenty of formulas and doses used in studies targeting redox therapies that make comparative analysis difficult. Moreover, there is also the placebo effect, which has been reported to be as high as 50%, interferes with proof of efficacy, although the ability to recognize treatment. In addition, the need to use many subjective measures such as patient-driven symptom rating scales is the key point in this field. Therefore, it is necessary to conduct randomized controlled studies to determine the efficacy of clinical use.

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Key Words: Neurodegeneration, Redox Therapy, Oxidative Stress, Review

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