1 *Review*

# 2 Monitoring the Redox Status in Multiple Sclerosis

3 **Masaru Tanaka [1,2] and László Vécsei [1,2,*]**

4 [1] MTA-SZTE, Neuroscience Research Group, Semmelweis u. 6, Szeged, H-6725 Hungary;
5 tanaka.masaru.1@med.u-szeged.hu
6 [2] Department of Neurology, Interdisciplinary Excellence Centre, Faculty of Medicine, University of Szeged,
7 Semmelweis u. 6, H-6725 Szeged, Hungary
8 * Correspondence: vecsei.laszlo@med.u-szeged.hu; Tel.: +36-62-545-351

9

10 **Abstract:** Worldwide, over 2.2 million people are suffered from multiple sclerosis (MS), a
11 multifactorial demyelinating disease of the central nervous system. MS is characterized by
12 multifocal inflammatory or demyelinating attacks associated with neuroinflammation and
13 neurodegeneration. The blood, cerebrospinal fluid, and postmortem brain samples of MS patients
14 evidenced the disturbance of reduction-oxidation (redox) homeostasis such as the alterations of
15 oxidative and antioxidative enzyme activities and the presence of degradation products. This
16 review article discussed the components of redox homeostasis including reactive chemical species,
17 oxidative enzymes, antioxidative enzymes, and degradation products. The reactive chemical species
18 covered frequently discussed reactive oxygen/nitrogen species, infrequently featured reactive
19 chemicals such as sulfur, carbonyl, halogen, selenium, and nucleophilic species that potentially act
20 as reductive as well as pro-oxidative stressors. The antioxidative enzyme systems covered
21 the nuclear factor erythroid-2-related factor 2 (NRF2)-Kelch-like ECH-associated protein 1 (KEAP1)
22 signaling pathway. The NRF2 and other transcriptional factors potentially become a biomarker
23 sensitive to the initial phase of oxidative stress. Altered components of the redox homeostasis in MS
24 were discussed in search of a diagnostic, prognostic, predictive, and/or therapeutic biomarker.
25 Finally, monitoring a battery of reactive chemical species, oxidative enzymes, antioxidative
26 enzymes and degradation products helps evaluate the redox status of MS patients, expediting
27 prolongation of remission, prevention of relapse, and thus building personalized treatment plans.

28 **Keywords:** oxidative stress; redox; antioxidant; multiple sclerosis; biomarker; neurodegenerative
29 disease; personalized medicine

30

## 31 1. Introduction

32     Multiple sclerosis (MS) is an immune-mediated demyelinating disease of the brain and spinal
33 cord, which suffers over 2.2 million people worldwide and affects primarily young adults from 20 to
34 40 years of age. After one to two decades many MS patients enter a progressive phase of the disease.
35 As survival has been improved, MS patients are suffered throughout adult life. Years lived with
36 disability begin to increase steeply early in the second decade of life and disability-adjusted life years
37 peak in the sixth decade of life [1]. MS encompasses a wide range of symptoms from motor and
38 autonomic dysfunctions to psychobehavioral disturbances including gait difficulties, paresthesia,
39 spasticity, vision problems, dizziness and vertigo, incontinence, constipation, sexual disturbances,
40 pain, cognitive and emotional changes, anxiety, and depression [2-5].
41     Several genetic susceptibility and environmental factors have been proposed to alter the risk of
42 developing MS, but the underlying cause of the disease remains unknown [6,7]. The most typical
43 pathomechanism involved in MS is simultaneous inflammatory and neurodegenerative processes
44 [8,9]. Main pathological findings of MS include the blood-brain barrier disruption, multifocal
45 inflammation, demyelination, oligodendrocyte loss, reactive gliosis, and axonal degeneration [10].

46  Multifocal immune-mediated destruction of myelin and oligodendrocytes leading to progressive
47  axonal loss is a main cause of neurological deficits in MS [11-13].
48       The diagnosis of MS is confirmed by the presence of two or more multifocal inflammatory or
49  demyelinating attacks in central nervous system (CNS) with objective clinical evidence, a single
50  attack with magnetic resonance imaging (MRI)-detected lesions and positive cerebrospinal fluid
51  (CSF) analysis, or insidious neurological progression with positive brain MRI or CSF analysis [14].
52  The symptomatic course classifies MS into four subtypes. Approximately 85% of MS patients have
53  alternating episodes of neurological disability and recovery which last for many years, termed
54  relapsing-remitting MS (RRMS). Almost 90% of RRMS patients progress to steady neurological
55  decline within 25 years, termed secondary progressive MS (SPMS). Nearly 10% of MS patients are
56  suffered from steady deterioration of neurological functions without recovery, termed primary
57  progressive MS (PPMS). As few as 5% of MS patients present progressive neurological deficits with
58  acute attacks with or without recovery, termed progressive-relapsing MS (PRMS) [15]. However,
59  PRMS is no longer considered a subtype of MS and now grouped into PPMS with active disease of
60  new symptoms or changes in MRI scan [16]. In addition, clinically isolated syndrome (CIS) is a single
61  episode of monofocal or multifocal neurological deficits that lasts at least 24 hours. CIS is one of the
62  MS disease courses [10].
63       As in other neurodegenerative diseases, MS is a clinically classified disease of CNS in which
64  multifactorial factors including genetic, environmental, socioeconomic, cultural, and personal
65  lifestyle, play an initial role to form a causative complex, eventually converging into  similar
66  pathognomonic clinical pictures [4]. Inflammatory and demyelinating attacks are unique
67  manifestations in MS, but different pathomechanisms govern the distinguished clinical courses in
68  each subtype of MS.
69       Currently there is no cure for MS. Disease modifying therapy is the mainstay of MS treatment.
70  Immunomodulators, immunosuppressors, and cytotoxic agents are main groups of medicine.
71  Immunomodulators such as interferon beta (IFN)-beta (β), glatiramer acetate (GA), and siponimod
72  are used for CIS. Short courses of high-dose corticosteroid methylprednisolone alleviate acute flare-
73  ups of RRMS, evidencing that an inflammatory process predominates in RRMS and relapse
74  prevention of RRMS [17,18]. Siponimod is indicated for RRMS [18]. For active RRMS monoclonal
75  antibodies alemtuzumab and ocrelizumab, and immunomodulator dimethyl fumarate, fingolimod,
76  and teriflunomide are prescribed besides IFN-β and GA. For highly active RRMS, cytotoxic agents
77  cladribine and mitoxantrone are indicated, besides immunomodulatory fingolimod, and monoclonal
78  antibodies, natalizumab and ocrelizumab. PPMS and SPMS are characterized by a neurodegenerative
79  process leading to a neural death [16]. An immunosuppressive monoclonal antibody ocrelizumab is
80  indicated for treatment of PPMS [19] and siponimod has been recently licensed for treatment  of
81  SPMS [18] (Table 1).

82       **Table 1.** Licensed disease-modifying drugs in multiple sclerosis [17,18,19,20,21,22].

| Class | Drugs | Indications |
|---|---|---|
| Immunomodulators | Interferon beta (IFN-β) | CIS |
| | | Active RRMS |
| | Methylprednisolone | acute flare-ups RRMS |
| | | Relapse prevention |
| | Glatiramer acetate (GA) | CIS |
| | | Active RRMS |
| | Dimethyl fumarate | Active RRMS |
| | Fingolimod | Active RRMS |
| | | High-active RRMS |
| | Teriflunomide | Active RRMS |
| | Siponimod | CIS |
| | | RRMS |
| | | SPMS |

| | Alemtuzumab | Active RRMS |
|---|---|---|
| **Immunosuppressors** | Natalizumab | High-active RRMS |
| | Ocrelizumab | Active RRMS<br>High-active RRMS<br>PPMS |
| **Cytotoxic Agents** | Cladribine | High-active RRMS |
| | Mitoxantrone | High-active RRMS |

83    Either a causative, accompanying, or resultant events of inflammation and neurodegeneration,
84    disturbance of redox metabolism has been observed and plays a crucial role in pathogenesis of MS
85    [23-25]. The serum proteomics revealed that ceruloplasmin, clusterin, apolipoprotein E, and
86    complement C3 were up-regulated in RRMS patients, compared to healthy controls. Vitamin D-
87    binding protein showed a progressive trend of oxidation and the increased oxidation of
88    apolipoprotein A-IV in progression from remission to relapse of MS [26]. CSF samples of patients in
89    a remission stage of RRMS showed higher purine oxidation product uric acid, reduced antioxidant,
90    and increased intrathecal synthesis of IgG [27]. The observations suggest the presence of redox
91    metabolism disturbance and involvement of inflammatory process in RRMS. Furthermore, higher
92    serum alpha ($\alpha$)-tocopherol levels were associated with reduced T1 gadolinium (Gd$^+$)-enhancing
93    lesions and subsequent T2 lesions in MRI of RRMS patients on IFN-β. Antioxidant glutathione (GSH)
94    mapping showed lower GSH concentrations in the frontoparietal region of patients suffered from
95    PPMS and SPMS than RRMS and no significant difference between those of RRMS and controls. Thus,
96    the oxidative stress in CNS was linked to neurodegeneration in progressive types of MS [28].

97    This review article reviewed participants of redox homeostasis including reactive chemical
98    species, oxidative and antioxidative enzymes, and resulting degradation products all of which serve
99    as evidence of biochemical assaults and tissue injuries under redox disequilibrium. Alterations of
100   redox components in MS in general, phase-, and treatment-specific components were reviewed in
101   search of a potential diagnostic, prognostic, predictive, and/or therapeutic redox biomarker. Finally,
102   monitoring different redox components including oxidative enzymes, antioxidative enzymes and
103   degradation products during the disease progression helps evaluate the redox status of MS patients,
104   thus expediting building the most proper personalized treatment plans for MS patients [29].

105   **2. Oxidative Stress**

106   A reduction oxidation (redox) reaction is a type of chemical reaction that involves the transfer of
107   electrons between two molecules. A pair of electrons transfers from a nucleophile to an electrophile,
108   forming a new covalent bond. The redox reaction is common and vital to the basic function of life
109   such as cellular respiration in which sugar is oxidized to release energy which is stored in ATP. Redox
110   metabolisms constitute multiple metabolic pathways involved in the series of redox chemical
111   reactions indispensable for sustaining life and, at same time, engaged in removal of electrophilic
112   oxidative species and other harmful nucleophiles. The dynamic activities range from a single electron
113   transfer, enzyme reaction, chemical reaction cascade, to signaling in cells, tissues, organ systems, and
114   whole organismal levels [30]. Oxidative stress is a state caused by an imbalance between the relative
115   levels of production of reactive oxidizing metabolites and their elimination by the enzymatic or non-
116   enzymatic antioxidant system. The oxidative state is induced by oxidative stressors either derived
117   from xenobiotics or produced from the activities of oxidative enzymes and essential cellular
118   constituents [31] (Figure 1 (a)). Oxidative stressors are linked to several neurologic and psychiatric
119   diseases including Alzheimer's disease (AD), Parkinson's disease (PD), MS, amyotrophic lateral
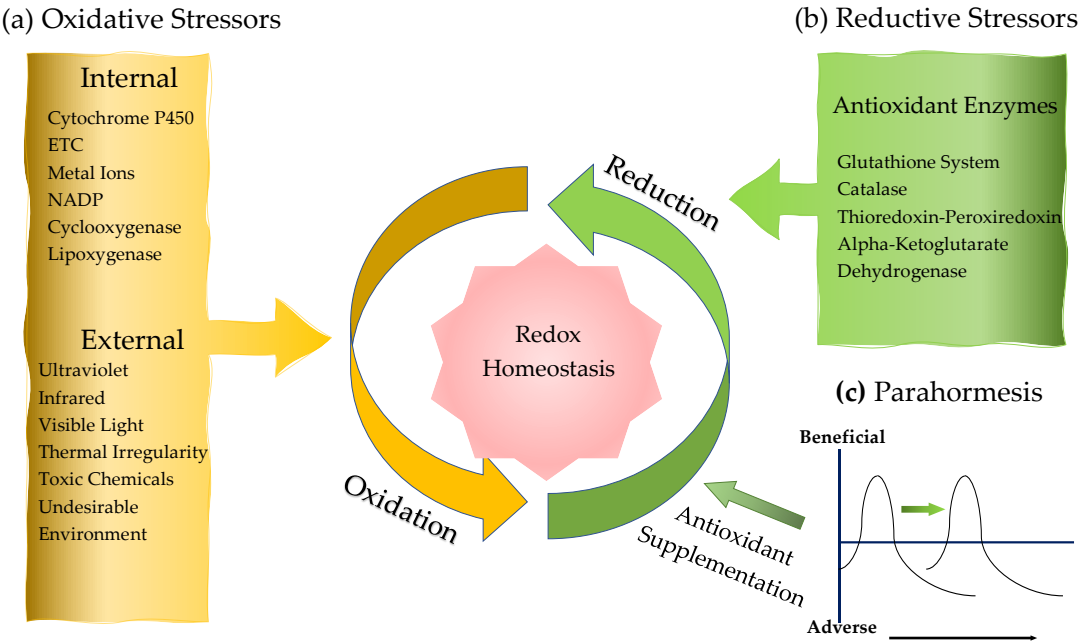120   sclerosis (ALS), and depression [32-36].

Internal

Cytochrome P450
ETC
Metal Ions
NADP
Cyclooxygenase
Lipoxygenase

External
Ultraviolet
Infrared
Visible Light
Thermal Irregularity
Toxic Chemicals
Undesirable
Environment

(b) Reductive Stressors

Antioxidant Enzymes

Glutathione System
Catalase
Thioredoxin-Peroxiredoxin
Alpha-Ketoglutarate
Dehydrogenase

Reduction

Redox
Homeostasis

Oxidation

**(c)** Parahormesis

Beneficial

Antioxidant
Supplementation

Adverse

**Figure 1.** Redox homeostasis and antioxidant supplementation. (a) Oxidative stressors comprise of external and internal stressors, exerting oxidative chemical reactions in organism. Oxidation is an indispensable bioenergetic process to sustain life. (b). Reductive stressors are products of antioxidative enzymes that generate antioxidants in response to regular oxidation activity and increased oxidative stress. (c) Antioxidant supplementation attempts to shift the biphasic response from adverse to beneficial phase to maintain nucleophilic tone. This mechanism is called parahormesis.

2.1. Endogenous oxidative stressors: oxidative enzymes and reactive species

Endogenous oxidative stressors are produced from cellular activities of cytosolic xanthine dehydrogenase (XDH), membrane-bound nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, inflammatory lipoxygenase (LOX) and cyclooxygenase (COX), phagocytic myeloperoxidase (MPO) in respiratory burst, a second messenger nitrogen oxide (NO)-producing nitric oxide synthetase (NOS), mitochondrial and lysosomal electron transfer chain (ETC) enzymes, among others. Transition metals such as iron ($Fe^{2+}$) and copper ($Cu^+$) also play a crucial role in the formation of oxidative stressors via the Fenton reaction [37].

2.1.1. Oxidative enzymes generating reactive oxygen species

Reactive oxygen species (ROS) include several free radicals such as superoxide ($O_2^{-\bullet}$) and hydroxyl radical ($OH^\bullet$) and nonradical molecules such as hydrogen peroxide ($H_2O_2$) and organic hydroperoxide (ROOH) (Table 1). ROS are produced in endogenously in the cytosol, the plasma membrane, the membranes of mitochondria and endoplasmic reticulum, peroxisomes, and phagocytic cells [38,39] (Figure 2). ROS is difficult for direct measurement in biological tissues due to its highly reactivity and short life.

**Table 2.** Reactive chemical species. During regular cellular activity living cells generate numerous reactive chemical species containing oxygen, nitrogen, sulfur, carbonyl, halogen, or selenium. Reactive sulfur species can contain thiols or nitrothiols. Free radicals possess at least one unpaired electron that makes highly reactive and short-lived. Nonradicals are oxidizing chemicals or easily converted to free radicals. Superoxide, reactive sulfur species, or reactive selenium species can be reducing agents as reactive nucleophilic species.

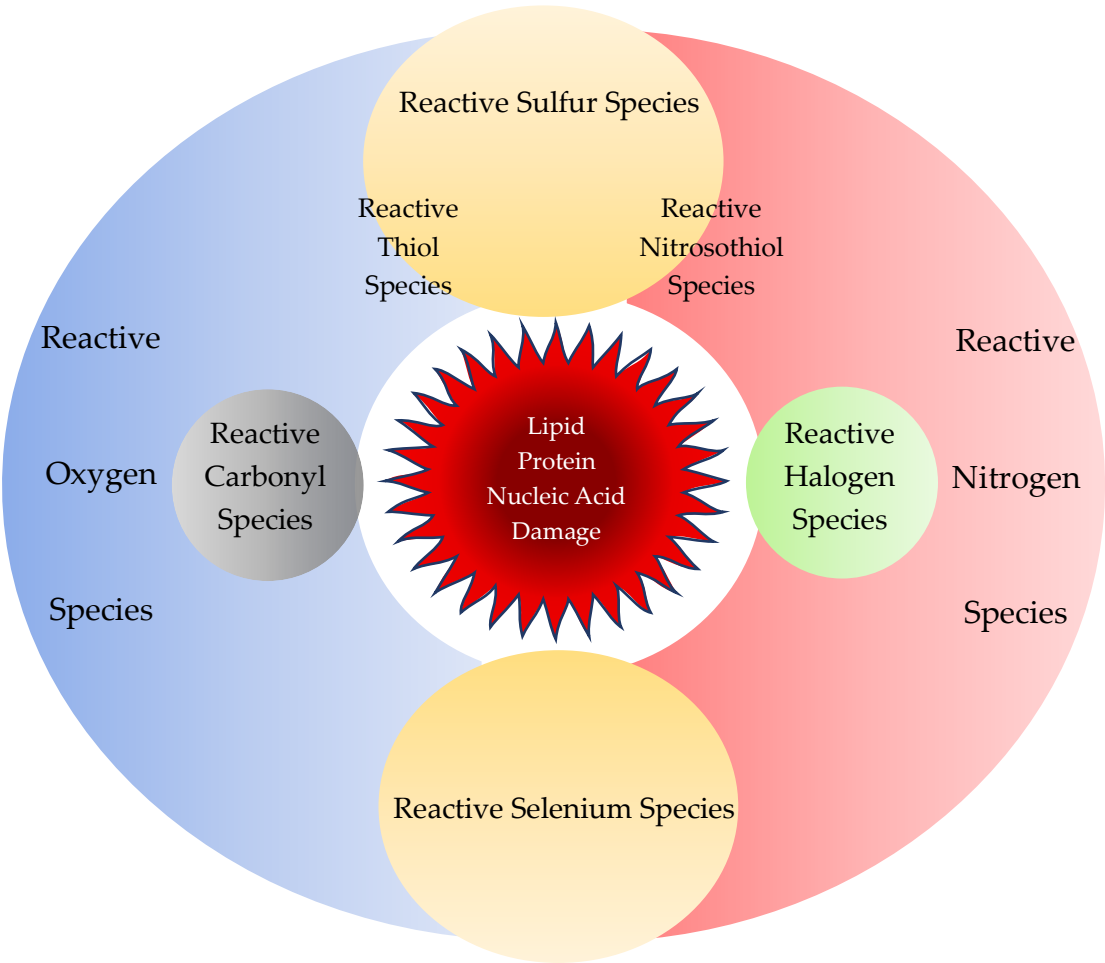| Reactive Chemical Species | |
|---|---|
| **Reactive Oxygen Species (ROS)** | *Free Radicals* |
| | Superoxide anion ($O_2^{-\bullet}$), Hydroxyl radical ($OH^\bullet$), Alkoxyl radical ($RO^\bullet$), Peroxyl radical ($ROO^\bullet$) |
| | *Nonradicals* |
| | Hydrogen peroxide ($H_2O_2$), Organic hydroperoxide ($ROOH$), Organic peroxide ($ROOR$), Singlet oxygen ($O_2^1\Delta_g$), Ozone ($O_3$) |
| **Reactive Nitrogen Species (RNS)** | *Free Radicals* |
| | Nitric oxide radical ($NO^\bullet$), Nitrogen dioxide radical ($NO_2^\bullet$) |
| | *Nonradicals* |
| | Nitrite ($NO_2^-$), Nitrate ($NO_3^-$), Nitroxyl anion ($NO^-$), Nitrosyl cation ($NO^+$), Peroxynitrite ($ONOO^-$), Peroxynitrate ($O_2NOO^-$), Nitrosoperoxycarbonate ($ONOOCO_2^-$), Dinitrogen trioxide ($N_2O_3$), Dinitrogen tetraoxide ($N_2O_4$), Nitryl chloride ($NClO_2$) |
| **Reactive Sulfur Species (RSN)** | *Free radicals* |
| | Thiyl radical ($RS^\bullet$), Peroxysulphenyl radical ($RSOO^\bullet$) |
| | *Nonradicals* |
| | Hydrogen sulfide ($H_2S$), Thiolate anion ($RS^-$), Thiol ($RSH$), Hydropersulfide ($RSSH$), Disulfide ($RSSR$), Hydropolysulfide ($RSS_nH$), Dialkyl polysulfide ($RSSnR$), Polysulfide ($H_2Sx$), Sulfenate ($RSO^-$), Sulfinate ($RSO_2^-$), Sulfonate ($RSO_3^-$), Thiosulmonate ($S_2O_3^{2-}$), Sulfite ($RS_2O_3^{2-}$), Sulfate ($SO_4^{2-}$), Thiosulfinate ($C_6H_{10}OS_2$), S-nitrosothiols ($RSNOs$), Nitrosopersulfide ($SSNO^-$), Dinitrosylated sulfite adduct ($SULFI/NO$) |
| **Reactive Carbonyl Species (RCS)** | *Nonradicals* |
| | Acetaldehyde ($CH_3CHO$), Acrolein (Proponel$^+$: $C_3H_4O$), Methylglyoxal 4-Hydroxy-nonenal ($C_9H_{16}O_2$), 3-Deoxyglucosone ($C_6H_{10}O_5$), Glyoxal ($C_2H_2O_2$), Methylgyoxal ($C_3H_4O_2$), Electronically excited triplet carbonyls ($^3L{=}O^*$) |
| **Reactive Halogen species (RHS)** | *Free radicals* |
| | Atomic chlorine ($Cl^\bullet$), Atomic bromine ($Br^\bullet$) |
| | *Nonradicals* |
| | Hypochlorite ($OCl^-$), Chloramines ($RNHCl$), Hypobromite ($OBr^-$), Hypoiodite ($IO^-$), Hypohalogenite ($XO^-$; $X = F, Cl, Br, or I$) |
| **Reactive Selenium Species (RSeS)** | *Nonradicals* |
| | Selenite ($O_3Se^{-2}$), Selenate ($SeO_4^{2-}$), Selenocysteine ($C_3H_7NO_2Se$), Selenomethionine ($C_5H_{11}NO_2Se$) |
| **Reactive Nucleophilic Species** | *Free radicals* |
| | Superoxide ($O_2^{-\bullet}$) |
| | *Noneradicals* |
| | Hydrogen sulfide ($H_2S$), Thiolate ($RS^-$), Hydropersulfide ($RSS^-$), Disulfide ($RSSR$), Selenite ($O_3Se^{-2}$), Selenate ($SeO_4^{2-}$), Selenocysteine ($C_3H_7NO_2Se$), Selenomethionine ($C_5H_{11}NO_2Se$) |

150

**Figure 2.** Reactive Chemical Species. Reactive chemical species comprise of not only reactive oxygen species and reactive nitrogen species, but also reactive sulfur, carbonyl, halogen, and selenium species. Sulfur reacts with oxygen or nitrogen to form reactive thiol or nitrosothiol species, respectively. All reactive chemical species react in concert during regular cellular activity but may cause oxidative stress to damage cellular components such as proteins, lipids, and nucleic acids.

In the cytosol, ROS can be generated by soluble intercellular components such as catecholamines, hydroquinones, flavins and thiols (RSHs) which undergo reduction reactions [40]. The cytosolic enzyme XDH normally catalyzes xanthine, $NAD^+$ and water ($H_2O$) to urate, reduced form of $NAD^+$, NADH and hydrogen ion ($H^+$). Reversible oxidation of cysteine residues or irreversible $Ca^{2+}$-stimulated proteolysis converts XDH to xanthine oxidase (XO) that transfers electrons to molecular oxygen ($O_2$), producing superoxide ($O_2^{-\bullet}$) during xanthine or hypoxanthine oxidation [41]. The serum levels of uric acid, a major endogenous antioxidant was measured in patients with PPMM, RRMM, and SPMM. The uric acid levels were significantly lower in active MS than inactive MS, and the uric acid levels were independently correlated with gender, disease activity and duration of the disease [42] (Table 3).

**Table 3.** Oxidative stress biomarkers of multiple sclerosis. The redox status can be monitored by the activities of oxidative and antioxidative enzymes and the presence of degradation products derived from cellular components. ↑: increase, ↓: decrease, -: unknown.

| Classes | Types | Human Samples | | Reference |
|---|---|---|---|---|
| | | **Blood** | **CSF** | |
| Reactive Species | Reactive Nitrogen Species | ↑ | ↑ | [75] |

| | | | | |
|---|---|---|---|---|
| Oxidative Enzymes | Xanthine Dehydrogenase (XHD) | ↓ | - | |
| | Nicotinamide Adenine Dinucleotide Phosphate (NADPH) Oxidase | ↑ ↓ | | [44] |
| | Superoxide Dismutase (SOD) | ↑ | ↓ | [58-61] |
| | Inducible Nitric Oxide Synthase (*i*NOS) | ↑ | ↑ | [16,91-93] |
| | Myeloperoxidase (MPO) | mixed | ? | [45] |
| Antioxidative Enzymes and Transcriptional Factors | Glutathione Peroxidase (GPx) | ↑ (relapse) ↓ (remission) | ↓ | [123-125,142-144] |
| | Glutathione Reductase (GSR) | - | ↑ | [144,145] |
| | Catalase | ↓ (granulocyte) | ? | [144,1452] |
| | Xanthine oxidase (XO)-Uric Acid | ↓ | - | [42] |
| | Nuclear Factor Erythroid 2-Related Factor (Nrf2) | ↑ | - | [61] |
| | Peroxisome proliferator-activated receptors (PPARs) | - | ↑ | [156] |
| | Peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1$\alpha$) | ↓ | - | [162] |
| Degradation Products and End Products | Protein | Protein carbonyls | ↑ | - | [168-170,176-179] |
| | | 3-nitrotyrosin (3-NO-Tyr) | ↑ | - | [175-179] |
| | | Protein glutathionylation | ? | - | [181] |
| | | Dityrosine | ↑ | - | [172] |
| | | Advanced oxidation protein products (AOPPs) | ↑ | - | [58,172,183] |
| | | Advanced glycation end products (AGEs) | ↑ | ↑ | [172,185] |
| | Amino acids | Asymmetric dimethylarginine (ADMA) | ↓ | - | [187] |
| | Lipid | F2-isoprostane (F2-isoP) | ↑ | ↑ | [190-194] |
| | | Malondialdehyde (MDA) | mixed | ↑ | [57,76,144,148,195] |
| | | 4-hydroxynonenal (4-HNE) | ? | ↑ | [196] |
| | | Hydroxyoctadecadienoic acid (HODE) | ↑ | ↑ | [197] |
| | | Oxysterol | ↑ or ↓ | ↑ | [199] |
| | DNA | 8-dihydro-2′ deoxyguanosine (8-oxodG) | ↑ | ? | [123] |

169   The plasma membrane is a network of phospholipid bilayer and integral proteins, which
170   protects the cellular organelles from the outer environment and responsible for several cellular
171   functions such as cell adhesion, ion transport, cell signaling and phagocytosis. The main ROS of the
172   plasma membrane is superoxide ($O_2^{-\bullet}$) produced by the membrane-bound enzyme nicotinamide
173   adenine dinucleotide phosphate oxidase (NOX) which is composed of two membrane proteins, three

174  cytosolic proteins, and a small GTP-binding protein [43,44]. The expression of NOX isoform NOX5
175  was significantly increased, but the expression NOX4 was significantly decreased in serum of RRMS
176  patients, suggesting differential NOX isoform expression contributes to OS-associated vascular
177  changes in MS [45]. ROS is also produced by COX and LOX which convert arachidonic acid to
178  prostaglandins, thromboxanes, and leukotrienes. Phospholipase $A_2$ generates ROS during
179  arachidonic acid oxidation [46]. In the presence of transition metal ions such as $Fe^{2+}$ and $Cu^+$,
180  hydrogen peroxide ($H_2O_2$), organic hydroperoxide (ROOH) and organic peroxide (ROOR) produce
181  hydroxyl ($OH^\bullet$), alkoxyl ($RO^\bullet$) and peroxyl radical ($ROO^\bullet$), respectively [47]. (Table 3).

182      Superoxide dismutase (SOD) catalyzes the disproportionation of two superoxide ($O_2^{-\bullet}$) into
183  molecular oxygen ($O_2$) and hydrogen peroxide ($H_2O_2$). These enzymes are present in almost all
184  aerobic cells and in extracellular fluids. SODs contain metal ion cofactors that, depending on the
185  isozyme, can be copper, zinc, manganese, or iron [48,49]. There are three isozymes in humans.
186  Dimeric copper- and zinc-coordinated SOD1 is in the cytoplasm; tetrameric manganese-coordinated
187  SOD2 is confined to the mitochondria; tetrameric copper- and zinc-coordinated SOD3 is extracellular
188  [50]. The mitochondrial ROS production takes place at four protein complexes, ubiquinone, and
189  cytochrome c of the ETC, embedded in the inner membrane of the mitochondria [51]. The Complexes
190  I/III/IV utilize NADH as the substrate, while Complexes II/III/IV use succinic acid. The complex II is
191  also glycerol 3-phosphate dependent. The primary mitochondrial ROS is superoxide ($O_2^{-\bullet}$) that is
192  converted by mitochondrial SOD into hydrogen peroxide ($H_2O_2$), which can be turned into hydroxyl
193  ($OH^\bullet$) via the Fenton reaction [52]. The Complex I and III release superoxide ($O_2^{-\bullet}$) into the
194  mitochondrial matrix where it can damage the mitochondrial DNA, while the Complex III also
195  releases superoxide ($O_2^{-\bullet}$) into the intermembrane space where it is accessible to the cytosol [53].
196  Reduced levels of antioxidant $\alpha$-tocopherol was observed in blood of patients with Leber's hereditary
197  optic neuropathy which is caused by mitochondrial mutation of the Complex I, suggesting that
198  oxidative load was elevated, and antioxidant capacity was compromised [54]. Other mitochondrial
199  enzymes which contribute to hydrogen peroxide ($H_2O_2$) production are monoamine oxidases,
200  dihydroorotate dehydrogenase, $\alpha$-glycerophosphate dehydrogenase and $\alpha$-ketoglutarate
201  dehydrogenase ($\alpha$-KGDH) complex. Succinate dehydrogenase also generate ROS [55].

202      Significantly higher mean activity of SOD in erythrocyte lysates was reported in RRMS than
203  controls. Interestingly, the SOD activity of CIS was higher than that of RRMS [56]. The SOD activity
204  was significantly lower in the erythrocyte lysates of RRSM patients upon relapse than controls but
205  increased following the intravenous administration of corticosteroid methylprednisolone and
206  remained higher during remission period than controls. The mean SOD activity of serum/plasma
207  samples was significantly higher in RRMS compared to control groups [57]. However, platelet SOD1
208  and SOD2 activity was unchanged in MS patients [58]. In contrast SOD activity was observed
209  significant low in CSF of CIS and RRMS patients despite significantly high activity of plasma SOD.
210  There were negative correlations between the erythrocyte SOD activity and disease duration and
211  expanded disability status scale (EDSS) in CIS and RRMS, between the erythrocyte SOD activity and
212  $Gd^+$ enhancement lesion volume in CIS patients [59]. These findings suggest SOD activity as possible
213  diagnostic and prognostic marker (Table 3, Table 4).

214      **Table 4.** Possible redox biomarkers in multiple sclerosis. Reactive chemical species, oxidative
215      enzymes, antioxidants, antioxidative enzymes, degradation products, and end products are potential
216      biomarkers for multiple sclerosis (MS). Diagnostic biomarkers allow early detection and secondary
217      prevention; prognostic biomarkers suggest the likely clinical course; predictive biomarkers predict
218      the response of MS patients to a specific therapy; and therapeutic biomarkers indicate a target for
219      therapy. CIS: clinically isolated syndrome, PPMS: primary progressive MS; RRMS: relapsing-
220      remitting MS, SPMS: secondary progressive MS, mixedMM: mixed population of MS.

| Class | Components | Biomarkers | | | |
| --- | --- | --- | --- | --- | --- |
| | | Diagnostic | Prognostic | Predictive | Therapeutic |

| | | | | | |
|---|---|---|---|---|---|
| Reactive Chemical Species | Total nitrite ($NO_2^-$)/nitrite ($NO_3^-$) value (tNOx) | PPMS, RRMS, Relapse, SPMS | RRMS | - | - |
| | *S*-nitrosothiol | RRMS, SPMS | Spinal injury | - | - |
| Oxidative Enzymes | Superoxide dismutase (SOD) | CIS, RRMS | CIS, RRMS | RRMS | RRMS |
| | Myeloperoxidase (MPO) | RRMS | RRMS | - | - |
| | Inducible nitric oxide synthase (*i*NOS) | RRMS | - | - | - |
| Antioxidants and Antioxidative Enzymes | Xanthine oxidase (XO)-Uric acid | PPMM, RRMM, SPMM | - | - | - |
| | Selenium | RRMS | - | - | - |
| | Glutathione reductase (GSR) | mixedMM | MixedMM | - | - |
| | Catalase | CIS, RRMS | RRMS | - | - |
| | Thioredoxin-Peroxiredoxin (TRX-PRDX) | MS | - | - | - |
| | Nuclear factor erythroid 2-related factor (Nrf2) | RRMS | - | RRMS | - |
| | Peroxisome proliferator-activated receptors (PPARs) | RRMS | - | - | - |
| | Peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1$\alpha$) | PPMS, SPMS | - | - | - |
| Degradation Products and End Products | Protein carbonyls | RRMS, SPMS | RRMS, SPMS | RRMS | - |
| | 3-Nitrotyrosine (3-NO-Tyr) | RRMS, SPMS | - | RRMS | - |
| | Glutathionylation | Acute attack | - | - | - |
| | Dityrosine | RRSM | - | - | - |
| | Advanced oxidation protein products (AOPPs) | CIS, RRMS | RRMS | RRMS | - |
| | Advanced glycation end products (AGEs) | RRMS | - | - | - |
| | Asymmetric dimethylarginine (ADMA) | RRMS, SPMS | - | - | - |
| | F2-isoprostane (F2-isoP) | RRMS, SPMS | SPMS | - | - |
| | Malondialdehyde (MDA) | RRMS | RRMS | RRMS | - |

| | | | | |
|---|---|---|---|---|
| 4-hydroxynonenal (4-HNE) | PPMS, RRMS, SPMS | - | - | - |
| Hydroxyoctadecadienoic acid (HODE) | CIS, RRMS | - | - | - |
| Oxocholesterols | MixedMS | SPMS | - | - |
| Oxidized low-density lipoprotein (oxLDL) | RRMS, SPMS | - | - | - |
| 8-OH2dG | RRMS | - | - | - |

The peripheral blood mononuclear cells (PBMCs) SOD1 proteins and mRNA expression were significantly lower in RRMS patients than controls and became significantly elevated following IFN-β1b treatment than the baseline [60]. These studies suggest SOD as a potential therapeutic biomarker (Table 4). However, the erythrocyte SOD activity remained unchanged following the treatment of natalizumab, a humanized monoclonal antibody against the cell adhesion molecule $\alpha$4-integrin. But levels of carbonylated protein and oxidized guanosine were reduced [61].

In the inner membrane of mitochondria and the endoplasmic reticulum, a heme-containing monooxygenase cytochrome P450 (CYP) enzymes are responsible for oxidizing steroids, cholesterols, and fatty acids. The CYPs forms ROS superoxide ($O_2^{-•}$) and hydrogen peroxide (ROOH) by substrate cycling [62]. Protonation of hydrogen peroxide (ROOH) forms hydrogen peroxide ($H_2O_2$), which, furthermore, cleaves into hydroxy radicals ($OH^•$). The redox cycling produces free radical semiquinone from quinoid substrates [63]. In the mitochondrial transport chain, flavoprotein reductase forms ROS by direct reduction of $O_2$ and via the mediation of quinones. [64]. Superoxide ($O_2^{-•}$) is produced by XO in the reperfusion phase of ischemia, LOX, COX, and NADPH-dependent oxidase [65]. In the endoplasmic reticulum NADH cytochrome b5 reductase can leak electrons to molecular oxygen ($O_2$) to generate superoxide ($O_2^{-•}$) during the NADPH-dependent oxidation of xenobiotics [66].

Most enzymes in the peroxisomes produce ROS during the catalysis of fatty acid $\alpha$- and $\beta$-oxidation, amino acid and glyoxylate metabolism, and synthesis of lipidic compounds. A large fraction of hydrogen peroxide ($H_2O_2$) generated inside peroxisomes was observed to penetrate the peroxisomal membrane and diffuse to the surrounding media [67]. The peroxide can diffuse through the channel formed by the peroxisomal membrane protein Pxmp2 and hydrogen peroxide ($H_2O_2$) generated by the peroxisomal urate oxidase can release through crystalloid core tubules into the cytosol [68]. Meanwhile, peroxisomes also possess protective mechanisms to counteract oxidative stress and maintain redox balance. Reduction in peroxisomal gene and protein expression was observed in MS grey matter [69].

The lysosomal ETC plays a central role to support the positive proton gradient to maintain an optimal pH of the acid hydrolases [70]. The ETC is made up of a flavin-adenine dinucleotide, a b-type cytochrome and ubiquinone with the donor NADH and ending to acceptor molecular oxygen ($O_2$), transferring three electrons. Superoxide ($O_2^{-•}$) is possibly produced in the acidic environment which favors dismutation of hydrogen peroxide ($H_2O_2$) into hydroxy radical ($OH^•$) by ferrous iron [71]. Furthermore, ozone ($O_3$) and ozone-like oxidants are generated from singlet oxygen ($O_2^1\Delta_g$) catalyzed by antibody or amino acid. Ozone ($O_3$) reacts with superoxide anion ($O_2^{-•}$) to form hydrogen peroxide ($H_2O_2$) in the presence of $Fe^{+2}$ [72].

2.1.2. Oxidative enzymes generating reactive nitrogen species

Reactive nitrogen species (RNS) are a group of nitrogen-congaing molecules including free radicals, nitric oxide (NO), and nitrogen dioxide ($NO_2$). Free radicals are nitric oxide ($NO^•$) and nitrogen dioxide ($NO_2^•$) radicals, while nonradicals are nitrite ($NO_2^-$) and nitrate ($NO_3^-$), among others (Table 2). RNS are derived from nitric oxide (NO) and superoxide anion ($O_2^{-•}$) produced by nitric oxide synthetase 2 (NOS2), NADPH oxidase, XO, LOX, and COX, among others [73,74]. At physiological concentrations, a gaseous molecule nitric oxide (NO) is a second messenger involved

262 in blood pressure regulation, smooth muscle relaxation, defense mechanisms, immune regulation,
263 and neurotransmission contributing the function of memory and learning [75].

264     Cross-sectional studies showed that the levels of nitric oxide metabolites nitrite ($NO_2^-$) and
265 nitrite ($NO_3^-$), measured as a total value (tNOx) are significant higher in plasma or serum of patients
266 with RRMS [76,77]. A longitudinal study revealed that higher serum tNOx is significantly correlated
267 with relapsing rate, suggesting prognostic biomarker of NOS [78]. Many studies of CSF samples
268 reported significantly higher levels of tNOx in RRMS and PPMS, compared to healthy controls
269 [79,80]. A study observed significantly higher levels of CSF tNOx in RRMS than SPMS, suggesting an
270 inflammatory role of RNS [81]. Significantly higher levels of CSF tNOx were reported in patients with
271 acute relapsing phase of RRMS than those with stable remitting phase of RRMS [82,83] (Table 3, Table
272 4).

273     In cGMP-dependent pathways, nitric oxide radical ($NO^{\bullet}$) generated by endothelial NOS in
274 endothelium, brain, and heart relaxes blood vessels and maintains normal blood pressure, while
275 nitric oxide radicals ($NO^{\bullet}$) produced by neuronal NOS serve as a neurotransmitter to regulate blood
276 pressure in the brain. Inducible NOS (*i*NOS) in macrophages and smooth muscle cells gives rise to
277 nitric oxide radicals ($NO^{\bullet}$) as in reaction to bacterial lipopolysaccharides and/or cytokines [84].

278     Nitric oxide radical ($NO^{\bullet}$) is produced from the metabolism of L-arginine by NOS that converts
279 L-arginine into L-citrulline and nitric oxide radical ($NO^{\bullet}$) by a 5-electron oxidation of a guanidine
280 nitrogen of L-arginine [85]. In mitochondria nitric oxide radicals ($NO^{\bullet}$) react with respiratory
281 Complex III to inhibit electron transfer and facilitate superoxide anion ($O_2^{\bullet-}$) production. The nitric
282 oxide radicals ($NO^{\bullet}$) also compete with molecular oxygen ($O_2$) for the binding site at the binuclear
283 center of cytochrome *c* oxidoreductase, inducing a reversible inhibition of cytochrome *c* oxidase.
284 Nitric oxide (NO) neutralizes ROS [41]. However, RNS react with oxygen molecules ($O_2$) and ROS,
285 giving rise to a variety of nitrogen oxides (NOs) such as nitrogen dioxide radical ($NO_2^{\bullet}$), nitrogen
286 dioxide ($NO_2$), dinitrogen trioxide ($N_2O_3$), peroxynitrite ($ONOO^-$), nitrite ($NO_2^-$), and nitrate ($NO_3^-$).
287 Higher concentrations of nitric oxide (NO) become toxic by forming nitrosothiols which oxidize
288 tyrosine, cysteine, methionine, and GSH. In mitochondria, nitric oxide radicals ($NO^{\bullet}$) inhibit
289 Complex I by *S*-nitrosation [86]. Together with other RNS this contributes the damage of cell
290 membranes, proteins, and lipid membrane leading to the degradation of mitochondria, lysosomes,
291 and DNA. The chain of events culminates in the inhibition of immune response and production of
292 carcinogenic nitrosamines [87]. Nitric oxide (NO) is also involved in metal homeostasis including Fe,
293 Cu, and Zn [88].

294     Highly toxic peroxynitrite ($ONOO^-$) is formed by the reaction of nitric oxide (NO) and
295 superoxide anions ($O_2^{-\bullet}$) leading to the production of more reactive compounds that oxidize
296 methionine and tyrosine residues of proteins, lipids, and DNA. Reacting with superoxide anion
297 ($O_2^{-\bullet}$), nitric oxide radicals ($NO^{\bullet}$) form peroxynitrite which causes reversible inhibition of cellular
298 respiration in the mitochondria [89]. In peroxisomes nitric oxide radicals ($NO^{\bullet}$) react with superoxide
299 anions ($O_2^{-\bullet}$) produced by XO to form peroxynitrite and hydrogen peroxides [67]. In addition, insulin
300 resistance favors peroxintrite formation [90].

301     In response to bacterial lipopolysaccharides and inflammatory stimuli, *i*NOS generates nitric
302 oxide (NO) that protects tissue hypoxia and serves as a neurotransmitter. However, overexpression
303 *i*NOS and subsequent increase of nitric oxide (NO) has been implicated in pathophysiology of
304 neurodegenerative diseases including MS [75]. The *i*NOS activity is upregulated in acute MS plaques
305 [17,91]. Increased activity and expression of *i*NOS in lymphocytes were found in active relapsing
306 phase of RRMS [92]. CSF *i*NOS expression was shown in MS patients and mean CSF NOS activity
307 was significantly higher, compared to controls [93] (Table 3).

308 2.1.3. Reactive sulfur species

309     Reactive sulfur species (RSS) are sulfur-based redox-active compounds able to oxidize or reduce
310 biomolecules under physiological conditions, often formed by thiols (RSHs) and disulfides (RSSHs).
311 RSS include cysteine and methionine, GSH, trypanothione, and mycothiol [94] (Table 2).

312    Thiyl radicals (RS$^\bullet$), very reactive oxidants produced in the active site of enzymes such as the
313    ribonucleotide reductase can react with nitric oxide radicals (NO$^\bullet$) [95]. Thiolate ions (RS$^-$) are better
314    nucleophiles than alkoxides because sulfur is more polarizable than oxygen [96]. Thiol (RSH) is a
315    metal ligand [97]. Hydrogen sulfide (H$_2$S) is produced from from L-cysteine by cistationine-γ-lyase.
316    Hydrogen sulfide (H$_2$S) increases the activity of *N*-methyl-D-aspartate receptor and β-adrenergic
317    receptors through a cAMP-dependent protein kinase and activates NOS and the hemoxygenase
318    favoring the formation of Nitric oxide (NO) and carbon monoxide (CO) from heme metabolism [98].
319    Hydrogen sulfide (H$_2$S) is a metal ligand that reacts with other biological electrophilic sulfur species
320    such as hydropersulfide (RSSR) and sulfenic acid (RSOH) [99]. Cysteine residues in GSH were found
321    to be readily oxidized by superoxide anions (O$_2$$^{-\bullet}$) to form singlet oxygen (O$_2$$^1$Δ$_g$), glutathione
322    disulfide (GSSG), and glutathione sulfonate (GSO$_3$$^-$) in a reaction involved with peroxysulphenyl
323    radical (RSOO$^\bullet$). This mechanism may apply to cysteine residues in proteins [100]. Hydroxyl radicals
324    (OH$^\bullet$) may also initiate the conversion of amino acids to peroxyl radicals [47]. Another reaction
325    catalyzed by XO is the decomposition of S-nitrosothiols (RSNO), a RNS, to nitric oxide (NO), which
326    reacts with a superoxide (O$_2$$^{-\bullet}$) anion to form peroxynitrite (ONOO$^-$) under aerobic conditions [101].
327    Hydropersulfide (RSSH) is a nucleophile as well as electrophilic molecule that is readily reduced to
328    extremely potent reductant thiol (RSH). Disulfide (RSSR) is electrophilic RSS that can be reduced to
329    thiol (RSH). Hydropolysulfide (RSS$_n$H) and dialkyl polysulfide (RSS$_n$R) are like hydropersulfide
330    (RSSH) [99]. RSS can interact with ROS, generating sulfur oxides such as peroxysulphenyl radical
331    (RSOO$^\bullet$), sulfenate (RSO$^-$), sulfinate (RSO$_2$$^-$), sulfonate (RSO$_3$$^-$), thiosulmonate (S$_2$O$_3$$^{2-}$), and SO$_4$$^{2-}$
332    [102]. Sulfenate (RSO$^-$) reacts with other thiols to give disulfides, RSSR. RSS can also interact with
333    RNS, leading to the formation of S-N hybrid molecules such as thiazate (NSO$^-$), thionitrite
334    (SNO$^-$) isomers, S-nitrosothiols (RSNOs), nitrosopersulfide (SSNO$^-$), and the dinitrosylated sulfite
335    adduct, SULFI/NO. S-nitrosothiols (RSNOs) can be reduced to thiol (RSH) and nitroxyl (HNO) [103].
336    XO catalyzes S-nitrosothiols (RSNOs) to nitric oxide (NO), which reacts with a superoxide (O$_2$$^{-\bullet}$)
337    anion to form peroxynitrite (ONOO$^-$) under aerobic conditions [85]. The properties of thiazate
338    (NSO$^-$), thionitrite (SNO$^-$) isomers, nitrosopersulfide (SSNO$^-$) and polysulfides
339    dinitrososulfites (Sulfi/NO) are to be determined and they appear to be a source of nitric oxide (NO)
340    and nitroxyl (HNO) [104-106] (Table 2).

341    An antioxidant *N*-acetyl cysteine administration was reported to improve cognitive functions in
342    patients in MS and *N*-acetyl cysteine supplement is under clinical trial for the treatment of fatigue in
343    MS patients [107,108]. The levels of methionine reported mixed results. The plasma methionine levels
344    were significantly reduced in RRMS and dietary methionine supplement was proposed for the
345    treatment [109]. The level of methionine sulfoxide was elevated more than two-fold in CSF of MM
346    patients and reduction of dietary methionine was reported to slow the onset and progression MM
347    [110,111]. The levels of GSH in MS have not reached a consensus [111-113]. Trypanothione and
348    mycothiol have not been investigated in MS. The serum *S*-nitrosothiol levels were increased in RRMS
349    and SPMS, and selectively correlated with spinal cord injury and thus a high level of *S*-nitrosothiol
350    is proposed to be a potential prognostic biomarker for spinal cord injury in MS [114] (Table 3,Table 4
351    ).

352    2.1.4 Reactive carbonyl/halogen/selenium species

353    Reactive carbonyl species (RCS) are metabolically generated highly reactive molecules with
354    aldehydes and electronically excited ($^3$L=O$^*$) triplet carbonyls known for their harmful reactions to
355    nucleic acids, proteins, and lipids [47]. In addition, RCS are considered to participate in electrophilic
356    signaling of adaptive cell response and post-transcriptional protein modification [115]. RCS are
357    classified into α,β-unsaturated aldehydes; keto-aldehyde and di-aldehydes. In the presence of
358    catalase and bicarbonate, XO was found to produce the strong one-electron oxidant carbonate radical
359    anion from oxidation with acetaldehyde. The carbonate radical was likely produced in one of the
360    enzyme's redox centers with a peroxymonocarbonate intermediate [41]. Self-reaction of lipid peroxyl
361    radical (LOO$^\bullet$) produced by the oxidation of polyunsaturated fatty acids (PUFAs) by hydroxyl radical
362    (HO$^\bullet$) generates electronically excited triplet carbonyls ($^3$L=O$^*$) yielding to singlet oxygen (O$_2$$^1$Δ$_g$) [43]

363    (Table 2). RCS react with amines and thiols leading to advanced glycation end products (AGEs),
364    biomarkers of ageing and degenerative diseases [116].
365          MPO, a lysosomal heme-containing enzyme present in granulocytes and monocytes catalyzes
366    the conversion of hypdrogen peoxide ($H_2O_2$) and chloride anion (Cl$^-$) to hypochlorous acid (HClO)
367    during the respiratory burst. An adipocyte producing hormone leptin stimulates the oxidative burst
368    [117]. MPO also oxidizes tyrosine to tyrosyl radical [118]. MPO mediates protein nitrosylation,
369    forming 3-chlorotyrosine (3-Cl-Tyr) and dityrosine crosslinks [119,120] (Table 2).
370          Studies on MPO activity reported mixed results. The mean MPO activity of peripheral leukocyte
371    was observed reduced in a mixed population of MS patients, compared to controls [121]. Significantly
372    higher serum MPO activity was measured in opticospinal phenotype (OSMS) of RRMS at relapse and
373    remission and in conventional phenotype of RRMS at remission, compared to controls. A positive
374    correlation was associated between Kurtzke's EDSS and MPO activity at remission of OSMS [122]
375    (Table 4). The mean MPO activity of peripheral leukocytes was found higher, but statistically not
376    significant in RRMS, compared to controls [123] (Table 3). No study regarding CSF MPO activity in
377    MS was found.Selenium is an essential micronutrient with similar chemical and physical properties
378    to sulfur, but more easily oxidized and kinetically more labile than sulfur. Selenium is a component
379    of proteinogenic selenocysteine, naturally occurring selenomethionine and selenoproteins such
380    as glutathione peroxidase (GPx), thioredoxin reductase (TRXR), and selenoprotein P. [124]. Reactive
381    selenium species (RSeS) are selenium-containing inorganic and organic compounds including
382    selenite ($O_3Se^{-2}$), selenocysteine ($C_3H_7NO_2Se$), and selenomethionine ($C_5H_{11}NO_2Se$) [125] (Table 2).
383    Selenium have both beneficial and harmful actions. At low concentration it works as an antioxidant,
384    inhibiting lipid peroxidation and detoxifying ROS as a component of GPx and TRXR, while at high
385    concentration it becomes a toxic pro-oxidant, generating ROS, inducing lipid oxidation and forming
386    cross-linking in thioproteins [126] (Table 2). The serum selenium levels were measured significantly
387    lower in MS patients, compared to controls, suggesting antioxidant capacity is impaired in MS [127]
388    (Table 3).

389    2.1.5. Exogenous oxidative factors

390          Oxidative stressors are generated in reaction to exogenous stimuli such as pollutants, food and
391    alcohol, cigarette smoke, heavy metals, chemotherapy, drug and xenobiotics, or radiation. Organic
392    solvents, organic compounds such as quinone, pesticides and heavy metals including lead, arsenic,
393    mercury, chromium, and cadmium are common sources of oxidative stressors [37]. Ultraviolet and
394    infrared-B radiations generate oxygen radicals endogenously [128] (Figure 1 (a)). The levels of serum
395    arsenic, malondialdehyde (MDA), and lactate were elevated and ferric-reducing activity of plasma
396    was reduced RRMS patients and the levels of serum lithium were significantly lower and the levels
397    of nitric oxide (NO) were higher in RRMS patients, compared to healthy controls, suggesting
398    environmental factors seem to play a role in pathogenesis of MS [129,130].

399    **3. Reductive Stress**

400    3.1. Reactive nucleophilic species

401          Endogenous reductive stressors include nucleophilic free radical, inorganic, and organic
402    molecules and antioxidative enzyme. (Figure 1 (b)).Superoxide ($O_2^{-\bullet}$) anion is one of reactive
403    nucleophilic species and powerful reducing agent under physiological conditions, which initiates
404    reaction cascades generating another ROS such as hydrogen peroxide ($H_2O_2$) and sulfur dioxide ($SO_2$)
405    derivatives. Hydrogen sulfide ($H_2S$), thiolate (RS$^-$), hydropersulfide (RSS$^-$) and disulfide (RSSR) are
406    reactive nucleophilic species that can participate in nucleophilic substitution in vivo [98]. Selenium is
407    more nucleophilic than sulfur due to its greater electron density. The selenol (RSeH) portion of
408    selenocysteine ($C_3H_7NO_2Se$) is ionized at physiological pH, making it more nucleophilic against
409    oxidative species [131,132] (Table 2).

410    3.2. Antioxidative enzymes

411     Reductive stress is induced by excessive levels of reductive stressors that results from an
412 elevation in GSH/GSSG ratio, $NAD^+$/NADH, $NADP^+$/NADPH and/or or overexpression of
413 antioxidative enzymatic systems such as the GSH system, catalase, thioredoxin-peroxiredoxin (TRX-
414 PRDX) system, $\alpha$-ketoglutarat dehydrogenase (GPDH), and glycerol phosphate dehydrogenase
415 [133,134]. The reductive stressors deplete reactive oxidative species and are harmful as oxidative
416 stressors and implicated in pathological processes in AD, PD, and sporadic motor neuron disease,
417 among others [135].

418     The GSH system consists of GSH, the enzymes for synthesis and recycling including gamma-
419 glutamate cysteine ligase, glutathione synthetase, glutathione reductase (GSR) and gamma glutamyl
420 transpeptidase, and the enzymes for metabolism and antioxidation including glutathione S-
421 transferase and GPx [136]. The GPx is an enzyme containing four selenium-cofactors that catalyzes
422 the reducion of hydrogen peroxide ($H_2O_2$) to water molecule ($H_2O$) and organic hydroperoxide
423 (ROOH) to alcohol (ROH) by converting reduced monomeric GSH to GSSG. Glutathione s-
424 transferases show high activity with lipid peroxides [137]. Eight isozymes are in the cytosol,
425 membrane and plasma, protecting the organisms from oxidative stress [138].

426     Most studies on peripheral blood GPx activity reported nonsignificant results in a mixed
427 population of MS [123,139-142]. However, lower mean GPx activity of erythrocyte lysates in
428 remission and higher mean GPx were reported in acute relapse of RRMS [143]. GPx activity in CSF
429 was found lower in MS patients [144]. The GSR activity of lymphocyte and granulocyte lysates were
430 not significantly different in MS, compared to controls. However, a significant correlation of GPx and
431 GRx was observed in controls, but not in MS [145]. Mean GRx activity of CSF was found significantly
432 higher in MS patients [144] (Table 3, Table 4).

433     Catalases a tetrameric heme- or manganese-containing dismutase that catalyzes the conversion
434 of two hydrogen peroxide ($H_2O_2$) molecules to water ($H_2O$) in the presence of small amount of
435 hydrogen peroxide. The cofactor is oxidized by one molecule of hydrogen peroxide and then
436 regenerated by transferring the bound oxygen to a second molecule of substrate. The enzyme is
437 located in the peroxisomes, the cytosol of erythrocytes, and the mitochondria, removing harmful
438 hydrogen peroxides to prevent cellular and tissue damage [146].

439     Studies on the catalase activity of peripheral blood samples reported equivocal results in MS.
440 The catalase activity of granulocyte lysates was found lower in MS patients, compared to controls
441 [147]. The activities of CSF and plasma catalase were found increased in CIS and RRMS patients,
442 compared to healthy controls, and MS patients with lower EDSS had higher plasma and CSF catalase
443 activities [148] (Table 3, Table 4).

444     In TRX-PRDX system PRDXs catalyze the reduction of $H_2O_2$ to $H_2O$. $H_2O_2$ oxidizes the
445 peroxidatic cysteine of PRDXs to protein sulfenic acid (PSOH), which can react with the thiol (SH)
446 group of the resolving cysteine to yield the formation of an inter-(typical) or intramolecular (atypical)
447 disulfide bond. TRX/TRXR system mediates the reduction of the PRDX disulfide bond. TRX reduced
448 state is maintained by the flavoenzyme TRXR in the presence of NADPH. When $H_2O_2$ exceeds the
449 normal levels, PRDXs are overoxidized from PSOH to protein sulfinic acids ($PSO_2H$). The latter can
450 be reduced back to the native form of the enzyme by sulfiredoxin (SRX) in the presence of ATP.
451 However, further oxidation of PRDXs to $PSO_3H$ is irreversible [149].

452     Serum Trx1 was significantly increased in the newly diagnosed MS patients, compared to
453 controls. *TRX1* and *APEX1* mRNA expressions were significantly higher in the newly diagnosed MS
454 patients, patients under INF-β treatment, and patients who received immunosuppressant
455 azathioprine or betamethasone, compared to healthy controls [150]. *PRDX2* mRNA is upregulated
456 and PRDX2 expression is higher in MS lesions white matter of autopsy tissue of patients its expression
457 level is positively correlated with the degree of inflammation and oxidative stress [151] (Table 3, Table
458 4).

459     $\alpha$-KGDH is a mitochondrial enzyme in Krebs cycle, which catalyzes $\alpha$-ketoglutarate, coenzyme
460 A and $NAD^+$ to succinyl-CoA, NADH and $CO_2$, transferring an electron to the respiratory chain [152].
461 KGNH activity is sensitive to redox status. $H_2O_2$ reversibly inhibits KGNH by glutathionylation of
462 lipoic acid cofactor, resulting reducing electron supply to the respiratory chain. A lipid peroxidation

463    product 4-hydroxy-2-nonenal (4-HNE) reacts with lipoic acid cofactor, inhibiting $\alpha$-KGDH activity
464    [153]. The pyruvate tolerance test showed higher activity of $\alpha$-KGDH in serum of MS patients [154].
465    However, reduced expression and activity of mitochondrial $\alpha$-KGDH was observed in demyelinated
466    axons that correlated with signs of axonal dysfunction (Table 3) [155].
467         $\alpha$-GPDH catalyzes the reversible redox conversion of dihydroxyacetone phosphate to sn-
468    glycerol 3-phosphate, linking carbohydrate and lipid metabolism. A loss of $\alpha$-GPDH in
469    oligodendrocytes were observed in chronic plaques of MS patients, suggesting the presence of
470    antioxidant capacity impairment [156] (Table 3).
471         Nrf2 is a transcriptional factor of the antioxidative enzyme genes including catalase, GPx, GRx,
472    glutathione S-transferase, and SOD. In response to oxidative stress, the Kelch-like ECH-associated
473    protein 1 (KEAP1) inhibits the ubiquitin-proteasome system in the cytosol and facilitates the
474    translocation of Nrf2 into the nucleus to bind to the *cis*-acting enhancer sequence of the promotor
475    region, the antioxidant response elements [157,158]. Activation of the Nrf2-Keap1 pathway has been
476    observed in various types of cancers, accompanied with reduced antioxidant capacity and elevated
477    oxidative stress and inflammation [159]. The cytoplasmic and nucleic Nrf2 protein expression of
478    PBMC was increased and correlated with clinical improvement in MS patients on 14-month course
479    of natalizumab, an $\alpha$4 integrin receptor blocker [70] (Table 3, Table 4).
480         Other transcriptional factors involved in energy metabolism have been investigated. Peroxisome
481    proliferator-activated receptors (PPARs) are a transcriptional factor of the gene regulating energy
482    metabolism including glucose metabolism, fatty acid oxidation, thermogenesis, lipid metabolism, and
483    anti-inflammatory response [160]. PPARs have attracted growing attention as promising targets of
484    many diseases such as diabetes and hyperlipidemia [161]. An isoform PPAR-gamma (PPAR-$\gamma$) was
485    elevated in CSF samples of MS, compared to controls [162]. Peroxisome proliferator-activated
486    receptor gamma coactivator 1-$\alpha$ (PGC-1$\alpha$) 4 integrin receptor blocker is a transcriptional coactivator
487    that regulates the genes involved in energy metabolism. Reduced PGC-1$\alpha$ expression was associated
488    with mitochondria changes and correlated with neural loss in MS [163] (Table 3, Table 4).

489    3.3. Exogenous antioxidative factors

490         A daily diet rich in naturally occurring polyphenolic antioxidants such as flavonoids and
491    phenolic acids are regularly recommended for disease prevention and antioxidant supplements such
492    as vitamin C, vitamin E, *N*-acetyl cysteine, L-carnitine and folic acid are frequently employed as a
493    complementary therapy for various diseases [164,165]. Those preventive and therapeutic measures
494    are based on the pathogenesis of diseases which are induced and developed under oxidative cellular
495    environment. However, unmonitored chronic antioxidant supplementation imposes reductive stress,
496    the counterpart of oxidative stress. The reductive stress-induced inflammation is observed in
497    hypertrophic cardiomyopathy, muscular dystrophy, pulmonary hypertension, rheumatoid arthritis,
498    AD, and metabolic syndrome [135]. In adipose tissue, furthermore, a long-term antioxidant
499    supplementation caused a paradoxical increase in oxidative stress which was associated with
500    mitochondrial dysfunction [166] (Figure 1 (c))
501         Vitamin supplements are recommended for the treatment of MS, as nutritional deficits are
502    frequently observed in patients with MS [167]. MS induced by reductive stress has not been reported,
503    but it deserves to monitor redox status in MS patients.

504    **4. Degradation Products Under Oxidative Stress**

505    *4.1. Proteins*

506         Protein carbonyls are degradation products of reactions between reactive species and proteins,
507    resulting in loss of function or aggregation. Quantification with 2,4-Dinitrophenylhydrazine products
508    showed increased carbonylation in plasma and serum of RRMS patients [168-170]. The plasma
509    carbonyl levels were elevated in SPMS and correlated with the EDSS, and the Beck Depression
510    Inventory [171]. The levels of carbonyl groups were elevated in serum of patients with RRMS and

511　lowered in the group of RRMS patients treated with INF-β [172]. The levels of CSF carbonyl proteins
512　measured were elevated in RRMS and progressive MS [173,174] (Table 3, Table 4).

513　　　A highly active RNS reacts with tyrosine residues of proteins to form nitrotyrosines, leading to
514　the alternation of protein conformation function. 3-nitrotyrosine (3-NO-Tyr) is the main product of
515　tyrosine oxidation, formed by the substitution of a hydrogen by a nitro group in the phenolic ring of
516　the tyrosine residues. 3-NO-Tyr content is assessed by western blotting, high-performance liquid
517　chromatography (HPLC), gas chromatography-mass spectrometry (GC/MS), and enzyme-linked
518　immunosorbent assay (ELISA) [175]. Mean 3-NO-Tyr was observed significantly higher in plasma
519　and serum of RRMS and SPMS patients and significantly higher 3-NO-Tyr was found in SPMS than
520　RRMS [169,176,177]. Decreased mean 3-NO-Tyr was reported following relapse and corticosteroid
521　treatment [178]. 3-NO-Tyr was found significantly lower in serum of MS patients following INF-β1b
522　treatment [179]. 3-NO-Tyr was found significantly reduced in peripheral leukocytes following GA
523　treatment [177] (Table 3, Table 4).

524　　　Protein glutathionylation is a redox-dependent posttranslational modification that results in the
525　formation of a mixed disulfide between GSH and the thiol group of a protein cysteine residue [180].
526　Protein glutathionylation is observed in response to oxidative or nitrosative stress and is redox-
527　dependent, being readily reversible under reducing conditions. Extracellular SOD, $\alpha$1-antitrypsin
528　and phospholipid transfer protein were found glutathionylated at cysteine residues in CSF of MS
529　Patients, witnessing the footprints of oxidative assault of MS [181].

530　　　Oxidative environments generate oxidized tyrosine orthologues such as o-tyrosine, m-tyrosine,
531　nitrotyrosine, and dityrosine. Dityrosine was elevated in serum of RRMS patients [172]. Advanced
532　oxidation protein products (AOPPs) are uremic toxins produced in reaction of plasma proteins with
533　chlorinated oxidants such as chloramines and hypochlorous acid (HClO) [182]. The levels of AOPPs
534　were significantly higher in plasma of MM patients [183]. The levels of AOPPs were significantly
535　higher in plasma and CSF of CIS and RRMS patients than healthy controls, and the AOPPs levels
536　were significantly higher CIS than RRMS. Furthermore, the levels of AOPPs were significantly higher
537　in patients with higher EDSS scores than lower ones [59]. The AOPPs levels were decreased in serum
538　of RRMS patients treated with IFN-β [172] (Table 3, Table 4).

539　　　AGEs are a group of glycotoxins produced in reaction of free amino groups of proteins, lipids,
540　or nucleic acids and carbonyl groups of reducing sugars. The AGEs can accumulate in tissues and
541　body fluids, resulting in protein malfunctions, reactive chemical production, and inflammation [184].
542　The levels of AGEs were significantly elevated in serum of RRMS patients, but no significant change
543　was observed after IFN-β treatment [172]. The concentrations of AGEs were significantly higher in
544　brain samples of MS patients, compared to nondemented counterparts. The levels of free AGEs were
545　correlated in CSF and plasma samples of MS patients, but not protein-bound AGEs [185] (Table 3,
546　Table 4).

547　*4.2. Amino Acids*

548　　　Asymmetric dimethylarginine (ADMA) is a L-arginine analogue produced in the cytoplasm in
549　the process of protein modification. The formation of ADMA is dependent on oxidative stress status.
550　ADMA is elevated by native or oxidized LDL and interferes with L-arginine in the production of
551　nitric oxide (NO) [186]. Significantly higher ADMA concentrations were observed in serum and CSF
552　of patients with RRMS and SPMS, while levels of arginine, L-homoarginine, nitrate, nitrite, ADMA
553　did not differ between patients with MS and healthy controls [187] (Table 3, Table 4).

554　*4.3. Lipid Membrane and lipoproteins*

555　　　Lipids in biological membrane are major target of OS. Peroxidation of lipid membrane is
556　initiated by ROS including superoxide anion ($O_2^{-\bullet}$), hydroxyl radical (OH$^\bullet$), hydrogen peroxide
557　($H_2O_2$), and singlet oxygen ($O_2^1\Delta_g$) and RNS including nitric oxide radical (NO$^\bullet$), peroxynitrite
558　(ONOO$^-$) and nitrite (NO$_2^-$) stealing electron from PUFAs such as arachidonic (20:4) and
559　docosahexaenoic acid (22:6). The abstraction of *bis*-allylic hydrogen of PUFA leads to the formation
560　of arachidonic acid hydroperoxyl radical (ROO$^\bullet$) and hydroperoxide (ROOH) in a chain reaction

561    manner [41]. A portion of arachidonic acid peroxides and peroxy radicals generate endoperoxides
562    rather than hydroperoxide (ROOH). The endoperoxides undergoes subsequent formation of a range
563    of bioactive intermediates such as F2-isoprostanes (F2-isoPs), MDA and 4-HNE. Hexanoyl-lysine
564    (HEL) adduct is a lipid peroxidation by-product which is formed by the oxidation of omega-6
565    unsaturated fatty acid, such as linoleic acid. Hydroxyoctadecadienoic acid (HODE) is derived from
566    the oxidation of linoleates, the most abundant PUFAs in vivo [188,189]. Meanwhile, a cyclic sugar
567    compound inositol is a major antioxidant component of the lipid membrane, which scavenges
568    reactive species [90].

569    Studies on blood F2-isoPs levels reported increases in MS, especially in RRMS and SPMS
570    subtypes compared to controls [190,191]. A study on CSF F2-isoPs levels presented three times higher
571    in patients with MS than ones with other neurologic diseases [192]. The levels of F2-isoPs were
572    moderately correlated with the degree of disability, suggesting a role as a prognostic marker [193].
573    MDA is highly reactive aldehyde generated by the reaction between reactive species and
574    polyunsaturated lipids to form adducts with protein or DNA [194]. Studies on blood or serum MDA
575    reported higher levels in MS patients [76,133]. The blood MDA levels were significantly higher in
576    RRMS than controls or CIS, higher in RRMS than in remission, and higher in remission than controls.
577    MDA levels were elevated at relapse, while lowered at day 5 of corticosteroid treatment [57,113].
578    Studies quantifying CSF MDA consistently reported higher levels in CIS and RRMS than controls
579    [57,149,144,195]. There are positive correlations between MDA levels of plasma and CSF, and MDA
580    levels in plasma/CSF and EDSS [148]. The levels of 4-HNE were elevated in the CSF of PPMS, RRMS,
581    and SPMS patients, particularly in PPMS [196]. No study regarding HEL in MS was found in
582    literature search. The serum13-HODE was identified as a part of metabolomic signatures associated
583    with more severe disease such as non-relapse-free MS or MS with higher EDSS [197]. The levels of 9-
584    HODE and 13-HODE were significantly increased in CSF of CIS and RRMS patients, compared to
585    healthy controls, but baseline levels of HODE did not differ between patients with signs of disease
586    activity during up to four years of follow-up and patients without MS [198] (Table 3, Table 4).

587    Cholesterol oxidization products oxysterols were studied. Levels of plasma oxysterols increased
588    in progressive MS patients and oxysterol levels were positively correlated with apolipoprotein C-II
589    and apolipoprotein E. Furthermore, oxysterol and apolipoprotein changes were associated with
590    conversion to SPMS [199]. Increased levels of oxidized low-density lipoprotein (oxLDL) in the
591    serum and higher serum levels of autoantibodies against oxLDL were reported in MS patients
592    [200,201]. Although studies on HDL levels in MS patients reported mixed results, lowered HDL
593    antioxidant function in MS patients was observed, suggesting the involvement of lipoprotein
594    function MS pathogenesis [200-203]. In mixed population of MS, decreased serum 24S-
595    hydroxycholesterol and 27-hydroxycholesterol and increased CSF lathosterol, compared to healthy
596    controls [204] (Table 3, Table 4).

597    *4.4. Nucleic acid*

598    8-Hydroxy-2'-deoxyguanosine (8-OH2dG) and 8-hydroxyguanosine (8-OHG) are biomarkers of
599    oxidative damage of nucleic acids, which can be assessed by ELISA, as well as by direct methods such
600    as HPLC and GC/MS [205,206]. Elevated levels of 8-OH2dG was reported in blood of RRMS patients.
601    DNA oxidation products were proposed as diagnostic biomarkers for MS [116] (Table 3, Table 4).

602    **5. Conclusion and Future Perspectives**

603    Redox biomarkers are classified by original cellular components and enzyme mechanisms of
604    action in redox homeostasis. Redox status can be assessed by the measurement of reactive chemical
605    species, oxidative or antioxidative enzyme activity, and degradation products derived from proteins,
606    amino acids, lipid membrane, and nucleic acids. Measurement of reactive chemical species and
607    oxidative enzyme activities assesses intensity of oxidative stress, while measurement of antioxidative
608    activity analyses compensatory capacity. Fine measurement of the various redox components may
609    reveal diagnostic, prognostic or predicative value to differentiate the disease status and progression
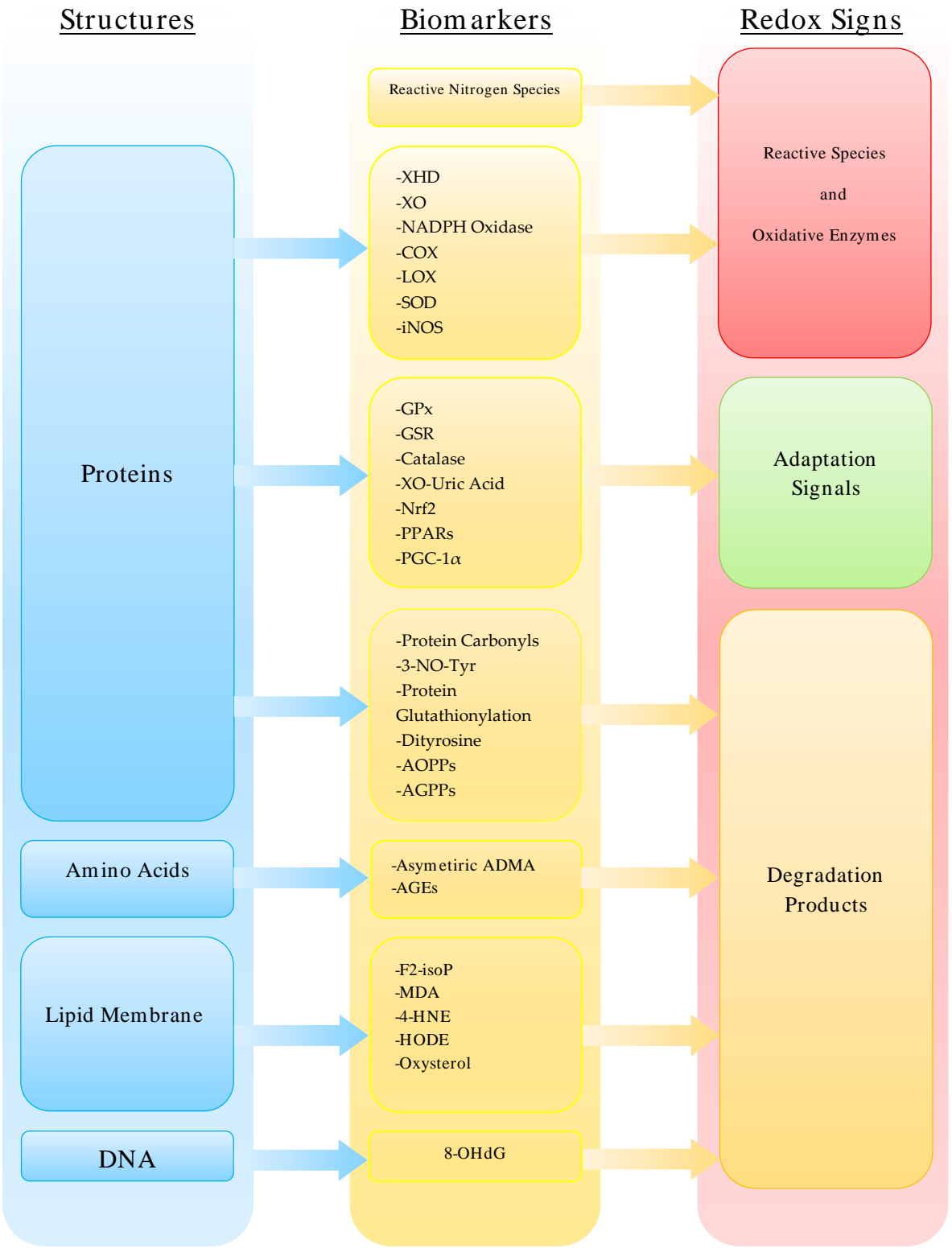610    (Figure 3).

**Figure 3.** Classification of Redox Biomarkers According to Cellular Structures, Biomarkers, and their Modes of Action in Redox Homeostasis.

The levels of nitric oxide (NO) metabolites, *S*-nitrosothiol, and the activities of oxidative enzymes including SOD, MPO, and *i*NOS have been found significantly different to patients with MS, compared to healthy controls. The levels of antioxidants including uric acid and selenium, activities of antioxidative enzymes including GSR, catalase, and TRX-PRDX, and concentrations of transcriptional factors Nrf2, PPARs, and PGC-1$\alpha$ have been found significantly changed in MS patients. The protein degradation products including protein carbonyls, 3-NO-Tyr, glutathionylation,

620  AOPPs, and AGEs, an amino acid by-product ADMA, the lipid and cholesterol degradation products
621  including F2-isoP, MDA, 4-HNE, HODE, oxocholesterols, and oxLDL, and the nucleic acid
622  degradation product 8-OH2dG significantly increased in samples of MS patients. Thus, the oxidative
623  enzymes, antioxidative enzymes, and redox degradation products have been identified as promising
624  biomarkers for the diagnosis of MS. Furthermore, SOD, 3-NO-Tyr, and MDA are sensitive to subtypes
625  of MS, CIS and RRMS, RRMS and SPMS, RRMS and remission, respectively. tNOx, *S*-nitrosothiol,
626  SOD, MPO, GSR, catalase, protein carbonyls, AOPPs, F2-isoP, MDA, and oxyocholesterols were
627  correlated with EDSS and thus they are potential prognostic biomarkers for MS. SOD, Nrf2, protein
628  carbonyls, 3-NO-Tyr, AOPPs, and MDA were observed sensitive to the treatment of MS, being
629  possible predictive biomarkers. Finally, SOD is a possible drug target of MS as a therapeutic marker
630  (Table 3).
631  In addition to biomarkers described above, search for novel biomarkers has become a growing
632  interest in neurodegenerative diseases. A micro RNA (miRNA) is a short non-coding RNA molecule
633  consisting of approximately 22 nucleotides, which functions in posttranscriptional gene silencing.
634  miRNAs have been linked to pathogenesis of various diseases including cancer, autoimmune
635  diseases, and neurodegenerative disease such as PD [207]. Dysregulated interactions of miRNAs have
636  been reported in mild cognitive impairment and AD. The associated genes were related to regulation
637  of ageing and mitochondria [208]. Dysregulations of various miRNAs have been observed in AD, PD,
638  Huntington's disease, and ALS and thus miRNAs were proposed to be potential diagnostic and
639  therapeutic biomarkers of neurodegenerative diseases [209]. The link between environmental factors
640  and miRNA dysregulations in MS was discussed [210]. Furthermore, miRNAs in blood and CSF
641  samples of patients with MS as diagnostic and prognostic biomarkers have been reviewed recently
642  [211].
643  Long Interspersed Nuclear Element-1 (LINE-1) is an autonomous non-long terminal
644  repeat retrotransposon that creates genomic insertions through a RNA intermediate. The increased
645  number of germline and somatic LINE-1s have been linked to the risk and progression of cancer as
646  well as neurodegenerative and psychiatric diseases. An increased burden of highly active
647  retrotranposition competent LINE-1s have been associated with the risk and progression of PD and
648  LINE-1s were proposed as possible therapeutic biomarkers that can be targeted by reverse
649  transcriptase [212]. Furthermore, LINE-1s was considered involved in irregular immune response
650  and participate in pathogenesis of MS [213].
651  Considering the dynamics of redox homeostasis, the amounts of reactive species, activities of
652  oxidative and antioxidative enzymes, and concentrations of degradation products presumably differ
653  during the progression of MS. The early phase presents an elevation of oxidative enzyme activity and
654  a subsequent elevation of the activity of counteracting antioxidative enzymes with unchanged levels
655  of degradation products. As the activity of antioxidative enzymes becomes compromised due to
656  increasing oxidative stress, the amount of degradation products gradually increases, while the
657  antioxidative enzyme activities slowly wane and fatigue. Eventually, the antioxidative response
658  exhausts with elevated activities of oxidative enzymes and elevated levels of degradation products
659  (Figure 4). Further studies and exploration into novel biomarkers are expected in search of a robust
660  battery of biomarkers indicative to the redox status, in order to realize a fine calibration of major
661  redox components that helps identify the disturbance of redox homeostasis, restore the nucleophilic
662  tone and the most importantly build the best personalized treatment of MS [214].
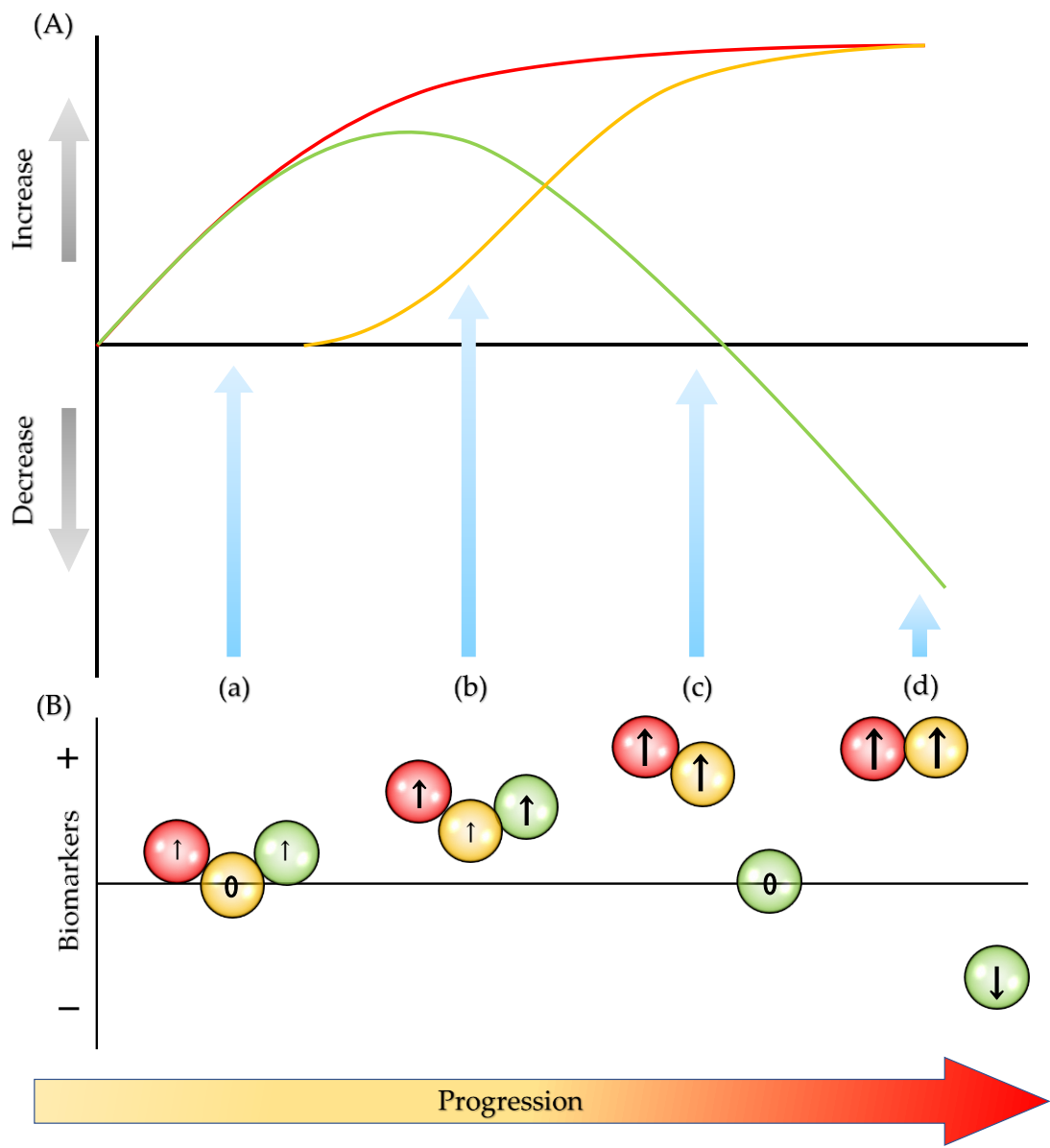
663

**Figure 4.** Dynamics of Redox Components in Disease Progression. (A) − (red line): Reactive chemical species and activities of oxidative enzymes increase gradually. − (orange line): The degradation products increase accordingly upon exhaustion of antioxidative enzymes' activities. − (green line): Antioxidative enzymes offset the effects of oxidative enzymes in the early phase, however; the antioxidative activities decline and, finally, fatigue in the later phase, resulting in the exacerbation of inflammation and cellular damage. (B) Biomarkers of three redox components may present different values. (a) The levels of oxidative enzyme slightly increase, but the degradation markers stay in a normal range. The antioxidative markers also slightly increase. (b) The oxidative markers further elevate, and the degradation markers start slightly increasing. The antioxidative markers also stay elevated. (c) The oxidative enzyme markers increase, but antioxidative markers return to normal range. The degradation product markers further elevate. (d) The oxidative markers greatly increase, but the antioxidative markers decline. The degradation products markers greatly elevate. ○ : oxidative biomarkers; ○ : degradation biomarkers; and ○ : antioxidative biomarkers.

**Author Contributions:** All authors read and agreed to the published version of the manuscript. Conceptualization, M.T. and L.V.; writing—original draft preparation, M.T.; writing—review and editing, M.T. and L.V.; visualization, M.T.; project administration, M.T.; supervision, L.V.; funding acquisition, L.V.

683    **Abbreviations**

| | |
|---|---|
| $\alpha$ | alpha |
| AD | Alzheimer's disease |
| ADMA | asymmetric dimethylarginine |
| AGEs | advanced glycation end products |
| ALS | amyotrophic lateral sclerosis |
| AOPPs | advanced oxidation protein products |
| $\beta$ | beta |
| CIS | clinically isolated syndrome |
| CNS | central nervous system |
| COX | cyclooxygenase |
| CSF | cerebrospinal fluid |
| CYP | cytochrome P450 |
| EDSS | expanded disability status scale |
| ELISA | enzyme-linked immunosorbent assay |
| ETC | electron transfer chain |
| F2-isoPs | F2-isoprostanes |
| GC/MS | gas chromatography-mass spectrometry |
| $Gd^+$ | gadolinium |
| GPx | glutathione peroxidase |
| GSH | glutathione |
| GSSH | glutathione disulfide |
| GA | glatiramer |
| GPDH | ketoglutarat dehydrogenase |
| GSR | glutathione reductase |
| HEL | hexanoyl-lysine |
| 4-HNE | 4-hydroxynonenal |
| HODE | hydroxyoctadecadienoic acid |
| HPLC | high-performance liquid chromatography |
| *i*NOS | inducible Nitric Oxide Synthase |
| IFN | Interferon |
| KEAP1 | Kelch-like ECH-associated protein 1 |
| KGDH | ketoglutarate dehydrogenase |
| LINE-1 | Long Interspersed Nuclear Element-1 |
| LOX | lipoxygenase |
| MDA | malondialdehyde |
| miRNA | micro RNA |
| MPO | myeloperoxidase |
| MRI | magnetic resonance imaging |
| MS | multiple sclerosis |
| $NAD^+$ | nicotinamide adenine dinucleotide |
| NADPH | nicotinamide adenine dinucleotide phosphate |
| NOS | nitric oxide synthetase |
| 3-NO-Tyr | 3-nitrotyrosine |
| NOX | nicotinamide adenine dinucleotide phosphate oxidase |
| Nrf2 | nuclear factor erythroid 2-related factor |
| 8-OH2dG | 8-Hydroxy-2′-deoxyguanosine |
| 8-OHG | 8-hydroxyguanosine |
| OSMS | opticospinal phenotype of relapsing-remitting multiple sclerosis |
| oxLDL | oxidized low-density lipoprotein |
| PD | Parkinson's disease |
| PGC-1 | peroxisome proliferator-activated receptor gamma coactivator 1 |
| PPARs | peroxisome proliferator-activated receptors |

| | |
|---|---|
| PUFAs | polyunsaturated fatty acids |
| RCS | reactive carbonyl species |
| redox | reduction oxidation |
| RHS | reactive halogen species |
| RNS | reactive nitrogen species |
| ROS | reactive oxygen species |
| PPMS | primary progressive multiple sclerosis |
| PRMS | progressive-relapsing multiple sclerosis |
| RRMS | relapsing-remitting multiple sclerosis |
| RSS | reactive sulfur species |
| RSeS | reactive selenium species |
| SOD | superoxide dismutase |
| SPMS | secondary progressive multiple sclerosis |
| tNOx | total value nitric oxide |
| TRX-PRDX | thioredoxin-peroxiredoxin |
| TRXR | thioredoxin reductase |
| XDH | xanthine dehydrogenase |
| XO | xanthine oxidase |

## References

1. GBD 2016 Neurology Collaborators. Global, regional, and national burden of neurological disorders, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol*. **2019**, *18(5)*, 459-480.

2. Fricska-Nagy, Z.; Füvesi, J.; Rózsa, C.; Komoly, S.; Jakab, G.; Csépány, T.; Jobbágy, Z.; Lencsés, G.; Vécsei, L.; Bencsik, K. The effects of fatigue, depression and the level of disability on the health-related quality of life of glatiramer acetate-treated relapsing-remitting patients with multiple sclerosis in Hungary. *Mult. Scler. Relat. Disord.* **2016**, *7*, 26-32.

3. Sandi, D.; Biernacki, T.; Szekeres, D.; Füvesi, J.; Kincses, Z.T.; Rózsa, C.; Mátyás, K.; Kása, K.; Matolcsi, J.; Zboznovits, D.; Burány, Z.; Langane, É.; Vécsei, L.; Bencsik, K. Prevalence of cognitive impairment among Hungarian patients with relapsing-remitting multiple sclerosis and clinically isolated syndrome. *Mult. Scler. Relat. Disord.* **2017**, *17*, 57-62.

4. Tanaka, M.; Toldi, J.; Vécsei, L. Exploring the Etiological Links behind Neurodegenerative Diseases: Inflammatory Cytokines and Bioactive Kynurenines. *Int. J. Mol. Sci.* **2020**, *21*, 2431.

5. Boeschoten, R.E.; Braamse, A.M.J.; Beekman, A.T.F.; Cuijpers, P.; van Oppen, P.; Dekker, J.; Uitdehaag, B.M.J. Prevalence of Depression and Anxiety in Multiple Sclerosis: A Systematic Review and Meta-Analysis. *J. Neurol. Sci.* **2017**, *372*, 331–341.

6. Waubant, E.; Lucas, R.; Mowry, E.; Graves, J.; Olsson, T.; Alfredsson, L.; Langer-Gould, A. Environmental and genetic risk factors for MS: an integrated review. *Ann. Clin. Transl. Neurol.* **2019**, *6(9)*, 1905–1922.

7. Biernacki, T.; Sandi, D.; Kincses, Z.T.; Füvesi, J.; Rózsa, C.; Mátyás, K.; Vécsei, L.; Bencsik, K. Contributing factors to health-related quality of life in multiple sclerosis. *Brain Behav.* **2019**, *9(12)*, e01466.

8. Rajda, C.; Majláth, Z.; Pukoli, D.; Vécsei, L. Kynurenines and Multiple Sclerosis: The Dialogue between the Immune System and the Central Nervous System. *Int. J. Mol. Sci.* **2015**, *6*, 16(8), 18270-18282.

9. Valles, S.L.; Burguet, F.; Iradi, A.; Aldasoro, M.; Vila, J.M.; Aldasoro, C.; Jordá, A. Astrocytes and Inflammatory Processes in Alzheimer's Disease. In *Glia in Health and Disease*.; Spohr, T., Ed.; IntechOpen; 2020; Available online: https://www.intechopen.com/books/glia-in-health-and-disease/astrocytes-and-inflammatory-processes-in-alzheimer-s-disease (24 June 2020).

10. Filippi, M.; Bar-Or, A.; Piehl, F.; Preziosa, P.; Solari, A.; Vukusic, S.; Rocca, M.A. Multiple sclerosis. *Nat Rev Dis Primers* **2018**, *4(43)*.

716  11.  Kincses, Z.T.; Tóth, E.; Bankó, N.; Veréb, D.; Szabó, N.; Csete, G.; Faragó, P.; Király, A.; Bencsik,
717       K.; Vécsei, L. Grey matter atrophy in patients suffering from multiple sclerosis. *Ideggyogy Sz.*
718       **2014**, *67(9-10)*, 293-300.

719  12.  Tóth, E.; Faragó, P.; Király, A.; Szabó, N.; Veréb, D.; Kocsis, K.; Kincses, B.; Sandi, D.; Bencsik,
720       K.; Vécsei, L.; Kincses, Z.T. The Contribution of Various MRI Parameters to Clinical and
721       Cognitive Disability in Multiple Sclerosis. *Front. Neurol.* **2019**, *9*, 1172.

722  13.  Andravizou, A.; Dardiotis, E.; Artemiadis, A.; Sokratous, M.; Siokas, V.; Tsouris, Z.; Aloizou,
723       A,M.; Nikolaidis, I. Bakirtzis, C.; Tsivgoulis, G.; Deretzi, G.; Grigoriadis, N.; Bogdanos, D.P.;
724       Hadjigeorgiou, G.M. Brain atrophy in multiple sclerosis: mechanisms, clinical relevance and
725       treatment options. *Autoimmun. Highlights* **2019**, *10(7)*.

726  14.  Hartung, H.P.; Graf, J.; Aktas, O.; Mares, J.; Barnett, M.H. Diagnosis of multiple sclerosis:
727       revisions of the McDonald criteria 2017 - continuity and change. *Curr. Opin. Neurol*. **2019**, *32(3)*,
728       327-337.

729  15.  Iacobaeus, E.; Arrambide, G.; Pia Amato, M.; Derfuss, T.; Vukusic, S.;  Hemmer, **B.**;  Tintore,
730       M.; Brundin, L.; 2018 ECTRIMS Focused Workshop Group. Aggressive multiple sclerosis (1):
731       Towards a definition of the phenotype. *Mult. Scler*. **2020**, 1352458520925369.

732  16.  Correale, J**.**; Marrodan, M**.**; Ysrraelit, M.C**.** Mechanisms of Neurodegeneration and Axonal
733       Dysfunction in Progressive Multiple Sclerosis. *Biomedicines* **2019**, *7(1)*, 14.

734  17.  Melendez-Torres, G.J**.**; Armoiry, X**.**; Court, R**.**; Patterson, J**.**; Kan, A**.**; Auguste, P**.**; Madan,
735       J**.**; Counsell, Carl**.**; Ciccarelli, O**.**; Clarke, A**.** Comparative effectiveness of beta-interferons and
736       glatiramer acetate for relapsing-remitting multiple sclerosis: systematic review and network
737       meta-analysis of trials including recommended dosages. *BMC Neurol*. **2018**, *18(1)***,** 162.

738  18.  Goodman, A.D.; Anadani, N.; Gerwitz, L. Siponimod in the treatment of multiple sclerosis.
739       *Expert Opin. Investig. Drugs* **2019**, *28(12)*, 1051-1057.

740  19.  Robertson, D.; Moreo, N. Disease-Modifying Therapies in Multiple Sclerosis: Overview and
741       Treatment Considerations. *Fed Pract.* **2016**, *33(6)*, 28-34.

742  20.  Hojati, Z; Kay, M.; Dehghanian, F. Mechanism of Action of Interferon Beta in Treatment of
743       Multiple Sclerosis. In Multiple Sclerosis, A Mechanistic View, 1st ed.; Minagar, A., Ed.;
744       Academic Press: 2016; pp. 365-392.

745  21.  Ziemssen T, Schrempf W. Glatiramer acetate: mechanisms of action in multiple sclerosis. *Int.*
746       *Rev. Neurobiol.* **2007**, *79*, 537-570.

747  22.  De Angelis, F.; John, N.A.; Brownlee, W.J. Disease-modifying therapies for multiple sclerosis.
748       *BMJ.* **2018**, *363*, k4674.

749  23.  Rajda, C.; Bergquist, J.; Vécsei L. Kynurenines, redox disturbances and neurodegeneration in
750       multiple sclerosis. *J. Neural. Transm. Suppl.* **2007**, *(72)*, 323-329.

751  24.  Rajda, C.; Pukoli, D.; Bende, Z.; Majláth, Z.; Vécsei L. Excitotoxins, Mitochondrial and Redox
752       Disturbances in Multiple Sclerosis. *Int. J. Mol. Sci*. **2017**, *18(2)*, 353.

753  25.  Sas, K.; Szabó, E.; Vécsei, L. Mitochondria, Oxidative Stress and the Kynurenine System, with a
754       Focus on Ageing and Neuroprotection. *Molecules* **2018**, *23(1)*, 191.

755  26.  Fiorini, A**.**; Koudriavtseva, T**.**; Bucaj, E**.**; Coccia, R**.**; Foppoli, C**.**; Giorgi, A**.**; Schininà, M.E**.**; Di
756       Domenico, F**.**; De Marco, F**.**; Perluigi, M**.** Involvement of oxidative stress in occurrence of
757       relapses in multiple sclerosis: the spectrum of oxidatively modified serum proteins detected by
758       proteomics and redox proteomics analysis. *PLoS One* **2013**, *8(6)***,** e65184.

759  27.  Choi, I.Y.; Lee, P.; Adany, P.; Hughes, A.J.; Belliston, S.; Denney, D.R.; Lynch, S.G. In vivo
760       evidence of oxidative stress in brains of patients with progressive multiple sclerosis. *Mult. Scler*.
761       **2018**, *24(8)*, 1029-1038.

762  28.  Barcelos, I.P.; Troxell, R.M.; Graves, J.S. Mitochondrial Dysfunction and Multiple
763       Sclerosis. *Biology* **2019**, *8*, 37.

764  29.  Cortese-Krott, M.M.; Koning, A.; Kuhnle, G.G.C.; Nagy, P.; Bianco, C.L.; Pasch, A.; Wink, D.A.;
765       Fukuto, J.M.; Jackson, A.A.; van Goor, H.; Olson, K.R.; Feelisch, M. The Reactive Species
766       Interactome: Evolutionary Emergence, Biological Significance, and Opportunities for Redox
767       Metabolomics and Personalized Medicine. *Antioxid. Redox Signal* **2017**, *27(10)*, 684-712.

768  30.  Santolini, J.; Wootton, S.A.; Jackson, A.A.; Feelisch, M. The Redox architecture of physiological
769       function. *Curr. Opin. Physiol.* **2019**, *9*, 34-47.
770  31.  Sies, H. On the history of oxidative stress: Concept and some aspects of current development.
771       *Curr. Opin. Toxicol.* **2018**, 7, 122-126.
772  32.  Viña, J; Lloret, A.; Vallés, SL.; Borrás, C.; Badía, MC.; Pallardó, F.V.; Sastre, J.; Alonso, M.D.
773       Mitochondrial oxidant signalling in Alzheimer's disease. *J. Alzheimers Dis.* **2007**, *11(2)*, 175-181.
774  33.  Pizzino, G.; Irrera, N.; Cucinotta, M.; Pallio, G.; Mannino, F.; Arcoraci, V.; Squadrito, F.; Altavilla,
775       D.; Bitto, A. Oxidative Stress: Harms and Benefits for Human Health. *Oxid. Med. Cell Longev.*
776       **2017**, *2017*, 8416763.
777  34.  Jorda, A.; Aldasoro, M.; Aldasoro, C.; Guerra-Ojeda, S.; Iradi, A.; Vila, J.M.; Campos-Campos, J.;
778       Valles, S.L. Action of low doses of Aspirin in Inflammation and Oxidative Stress induced by a$\beta_{1-42}$
779       on Astrocytes in primary culture. *Int. J. Med. Sci.* **2020**, *17(6)*, 834-843.
780  35.  Frijhoff, J.; Winyard, P.G.; Zarkovic, N.; Davies, S.S.; Stocker, R.; Cheng, D.; Knight, A.R.; Taylor,
781       E.L.; Oettrich, J.; Ruskovska, T.; Gasparovic, A.C.; Cuadrado, A.; Weber, D.; Poulsen, H.E.;
782       Grune, T.; Schmidt, H.H.; Ghezzi, P. Clinical Relevance of Biomarkers of Oxidative Stress.
783       *Antioxid. Redox Signal* **2015**, *23(14)*, 1144-1170.
784  36.  Tanaka, M.; Bohár, Z.; Vécsei, L. Are Kynurenines Accomplices or Principal Villains in
785       Dementia? Maintenance of Kynurenine Metabolism. *Molecules* **2020**, *25*, 564.
786  37.  Bhattacharyya, A.; Chattopadhyay, R.; Mitra, S.; Crowe S.E. Oxidative Stress: An Essential Factor
787       in the Pathogenesis of Gastrointestinal Mucosal Diseases. *Physiol. Rev.* **2014**, *94(2)*, 329–354.
788  38.  Aguilera, G, Colín-González, A.L.; Rangel-López, E.; Chavarría, A.; Santamaría, A. Redox
789       Signaling, Neuroinflammation, and Neurodegeneration. *Antioxid. Redox Signal.* **2018**, *28(18)*,
790       1626-1651.
791  39.  Lushchak, V.I. Free radicals, reactive oxygen species, oxidative stress and its classification. *Chem.*
792       *Biol. Interact.* **2014**, *224*, 164-175.
793  40.  Di Meo, S.; Reed, T.T.; Venditti, P.; Victor, V.M. Role of ROS and RNS Sources in Physiological
794       and Pathological Conditions. *Oxid. Med. Cell Longev.* **2016**, *2016*, 1245049.
795  41.  Collin, F. Chemical Basis of Reactive Oxygen Species Reactivity and Involvement in
796       Neurodegenerative Diseases. *Int. J. Mol. Sci.* **2019**, *20*, 2407.
797  42.  Drulovic. J.; Dujmovic, I.; Stojsavljevic, N.; Mesaros, S.; Andjelkovic, S.; Miljkovic, D.; Peric, V.;
798       Dragutinovic, G.; Marinkovic, J.; Levic, Z.; Mostarica Stojkovic, M. Uric acid levels in sera from
799       patients with multiple sclerosis. *J. Neurol.* **2001**, *248(2)*, 121–126.
800  43.  Prasad, A.; Balukova, A.; Pospíšil, P. Triplet Excited Carbonyls and Singlet Oxygen Formation
801       During Oxidative Radical Reaction in Skin. *Front. Physiol.* **2018**, *9*, 1109.
802  44.  Nordzieke, D.E.; Medraño-Fernandez, I. The Plasma Membrane: A Platform for Intra- and
803       Intercellular Redox Signaling. *Antioxidants* **2018**, *7*, 168.
804  45.  Doğan, H.O.; Yildiz, Ö.K. Serum NADPH oxidase concentrations and the associations with iron
805       metabolism in relapsing remitting multiple sclerosis. *J. Trace Elem. Med. Biol.* **2019**, *55*, 39-43.
806  46.  Yahfoufi, N.; Alsadi, N.; Jambi, M.; Matar, C. The Immunomodulatory and Anti-Inflammatory
807       Role of Polyphenols. *Nutrients* **2018**, *10*, 1618.
808  47.  Azadmanesh, J.; Borgstahl, G.E.O. A Review of the Catalytic Mechanism of Human Manganese
809       Superoxide Dismutase. *Antioxidants* **2018**, *7*, 25.
810  48.  Pospíšil, P.; Prasad, A.; Rác, M. Mechanism of the Formation of Electronically Excited Species by
811       Oxidative Metabolic Processes: Role of Reactive Oxygen Species. *Biomolecules* **2019**, *9*, 258.
812  49.  Di Marzo, N.; Chisci, E.; Giovannoni, R. The Role of Hydrogen Peroxide in Redox-Dependent
813       Signaling: Homeostatic and Pathological Responses in Mammalian Cells. *Cells* **2018**, *7*, 156.
814  50.  Case, A.J. On the Origin of Superoxide Dismutase: An Evolutionary Perspective of Superoxide-
815       Mediated Redox Signaling. *Antioxidants* **2017**, *6*, 82.
816  51.  Azadmanesh, J.; Borgstahl, G.E.O. A Review of the Catalytic Mechanism of Human Manganese
817       Superoxide Dismutase. *Antioxidants* **2018**, *7*, 25.
818  52.  Weidinger, A.; Kozlov, A.V. Biological Activities of Reactive Oxygen and Nitrogen Species:
819       Oxidative Stress *versus* Signal Transduction. *Biomolecules* **2015**, *5*, 472-484.

820    53.   Ježek, J.; Cooper, K.F.; Strich, R. Reactive Oxygen Species and Mitochondrial Dynamics: The Yin
821          and Yang of Mitochondrial Dysfunction and Cancer Progression. *Antioxidants* **2018**, *7*, 13.
822    54.   Klivenyi, P.; Karg, E.; Rozsa, C.; Horvath, R.; Komoly, S.; Nemeth, I.; Turi, S.; Vecsei, L. alpha-
823          Tocopherol/lipid ratio in blood is decreased in patients with Leber's hereditary optic neuropathy
824          and asymptomatic carriers of the 11778 mtDNA mutation. *J. Neurol. Neurosurg. Psychiatry* **2001**,
825          *70(3)*, 359-362.
826    55.   Ahmad, W.; Ijaz, B.; Shabbiri, K.; Ahmed, F.; Rehman, S. Oxidative toxicity in diabetes and
827          Alzheimer's disease: mechanisms behind ROS/ RNS generation. *J. Biomed. Sci.*, **2017**, *24(1)*, 76.
828    56.   Ljubisavljevic, S.; Stojanovic, I.; Cvetkovic, T.; Vojinovic, S.; Stojanov, D.;   Stojanovic, D.;
829          Stefanovic, N.; Pavlovic, D. Erythrocytes' antioxidative capacity as a potential marker of
830          oxidative stress intensity in neuroinflammation. *J. Neurol. Sci.* **2014**, *337(1-2)*, 8-13.
831    57.   Mitosek-Szewczyk, K.; Gordon-Krajcer, W.; Walendzik, P.; Stelmasiak, Z. Free radical
832          peroxidation products in cerebrospinal fluid and serum of patients with multiple sclerosis after
833          glucocorticoid therapy. *Folia Neuropathol*, **2010**, *48(2)*, 116-122.
834    58.   Inarrea, P.; Alarcia, R.; Alava, M.A.; Capablo, J.L.; Casanova, A.; Iñiguez, C.;   Iturralde, M.;
835          Larrodé, P.; Martín, J.; Mostacero, E.;   Ara, J.R. Mitochondrial complex enzyme activities and
836          cytochrome C expression changes in multiple sclerosis. *Mol. Neurobiol.* **2014**, *49(1)*, 1-9.
837    59.   Ljubisavljevic, S.; Stojanovic, I.; Vojinovic, S.; Stojanov, D.; Stojanovic, S.; Cvetkovic, T.; Savic,
838          D.; Pavlovic, D. The patients with clinically isolated syndrome and relapsing remitting multiple
839          sclerosis show different levels of advanced protein oxidation products and total thiol content in
840          plasma and CSF. *Neurochem. Int.* **2013**, *62(7)*, 988-997.
841    60.   Damiano, S.; Sasso, A.; De Felice, B.; Terrazzano, G.; Bresciamorra, V.;   Carotenuto, A.;
842          Orefice , N.S.; Orefice, G.; Vacca, G.; Belfiore, A.; Santillo, M.; Mondola, P. The IFN-beta 1b effect
843          on Cu Zn superoxide dismutase (SOD1) in peripheral mononuclear blood cells of relapsing-
844          remitting multiple sclerosis patients and in neuroblastoma SK-N-BE cells. *Brain Res. Bull.* **2015**,
845          *118*, 1-6.
846    61.   Tasset, I.; Bahamonde, C.; Agüera,; E, Conde, C.;   Cruz, A.H.; Pérez-Herrera, A.; Gascón, F.;
847          Giraldo, A.I.;   Ruiz, M.C.; Lillo, R.; Sánchez-López, F.; Túnez, I. Effect of natalizumab on
848          oxidative damage biomarkers in relapsing-remitting multiple sclerosis. *Pharmacol. Rep.* **2013**,
849          *65(3)*, 624-631.
850    62.   Spinello, A.; Ritacco, I.; Magistrato, A. The Catalytic Mechanism of Steroidogenic Cytochromes
851          P450 from All-Atom Simulations: Entwinement with Membrane Environment, Redox Partners,
852          and Post-Transcriptional Regulation. *Catalysts* **2019**, *9*, 81.
853    63.   Irazabal, M.V.; Torres, V.E. Reactive Oxygen Species and Redox Signaling in Chronic Kidney
854          Disease. *Cells* **2020**, *9*, 1342.
855    64.   Onukwufor, J.O.; Berry, B.J.; Wojtovich, A.P. Physiologic Implications of Reactive Oxygen
856          Species    Production    by    Mitochondrial   Complex    I   Reverse    Electron
857          Transport. *Antioxidants* **2019**, *8*, 285.
858    65.   Aggarwal, V.; Tuli, H.S.; Varol, A.; Thakral, F.; Yerer, M.B.; Sak, K.; Varol, M.; Jain, A.; Khan,
859          M.A.; Sethi, G. Role of Reactive Oxygen Species in Cancer Progression: Molecular Mechanisms
860          and Recent Advancements. *Biomolecules* **2019**, *9*, 735.
861    66.   Siendones, E.; Ballesteros, M.; Navas, P. Cellular and Molecular Mechanisms of Recessive
862          Hereditary Methaemoglobinaemia Type II. *J. Clin. Med.* **2018**, *7*, 341.
863    67.   Lismont, C.; Revenco, I.; Fransen, M. Peroxisomal Hydrogen Peroxide Metabolism and Signaling
864          in Health and Disease. *Int. J. Mol. Sci.* **2019**, *20*, 3673.
865    68.   Chu, R.; Lin, Y.; Reddy, K.C.; Pan, J.; Rao, M.S.; Reddy, J.K.; Yeldandi, A.V. Transformation of
866          epithelial cells stably transfected with $H_2O_2$-generating peroxisomal urate oxidase. *Cancer Res.*
867          **1996**, *56*, 4846–4852.
868    69.   Gray, E.; Rice, C.; Hares, K.; Redondo, J.; Kemp, K.; Williams, M.; Brown, A.; Scolding, N.;
869          Wilkins A. Reductions in neuronal peroxisomes in multiple sclerosis grey matter. *Mult. Scler.*
870          **2014**, *20(6)*, 651-659.

70. Lin, K.-J.; Lin, K.-L.; Chen, S.-D.; Liou, C.-W.; Chuang, Y.-C.; Lin, H.-Y.; Lin, T.-K. The Overcrowded Crossroads: Mitochondria, Alpha-Synuclein, and the Endo-Lysosomal System Interaction in Parkinson's Disease. *Int. J. Mol. Sci.* **2019**, *20*, 5312.

71. Chobot, V.; Hadacek, F.; Kubicova, L. Effects of Selected Dietary Secondary Metabolites on Reactive Oxygen Species Production Caused by Iron(II) Autoxidation. *Molecules* **2014**, *19*, 20023-20033.

72. Onyango, A.N. Endogenous Generation of Singlet Oxygen and Ozone in Human and Animal Tissues: Mechanisms, Biological Significance, and Influence of Dietary Components. *Oxid. Med. Cell Longev.* **2016**, *2016*, 2398573.

73. Adams, L.; Franco, M.C.; Estevez, A.G. Reactive nitrogen species in cellular signaling. *Exp Biol Med (Maywood)* **2015**, *240(6)*, 711–717.

74. Marrocco, I.; Altieri, F.; Peluso, I. Measurement and Clinical Significance of Biomarkers of Oxidative Stress in Humans. *Oxid. Med. Cell Longev.* **2017**, *2017*, 6501046.

75. Nasyrova, R.F.; Moskaleva, P.V.; Vaiman, E.E.; Shnayder, N.A.; Blatt, N.L.; Rizvanov, A.A. Genetic Factors of Nitric Oxide's System in Psychoneurologic Disorders. *Int. J. Mol. Sci.* **2020**, *21*, 1604.

76. Tavazzi, B.; Batocchi, A.P.; Amorini, A.M.; Nociti, V.; D'Urso, S.; Longo, S.; Gullotta, S.; Picardi, M.; Lazzarino G. Serum Metabolic Profile in Multiple Sclerosis Patients. *Mult. Scler. Int.* **2011**, *2011*, 167156.

77. Rejdak, K.; Petzold, A.; Stelmasiak, Z.; Giovannoni, G. Cerebrospinal fluid brain specific proteins in relation to nitric oxide metabolites during relapse of multiple sclerosis. *Mult. Scler.* **2008**, *14(1)*, 59-66.

78. Giovannoni, G.; Miller, D.H.; Losseff, N.A.; Sailer, M.; Lewellyn-Smith, N.; Thompson, A.J.; Thompson, E.J. Serum inflammatory markers and clinical/MRI markers of disease progression in multiple sclerosis. *J. Neurol.* **2001**, *248(6)*, 487-495.

79. Peltola, J.; Ukkonen, M.; Moilanen, E.; Elovaara, I. Increased nitric oxide products in CSF in primary progressive MS may reflect brain atrophy. *Neurology* **2001**, *57(5)*, 895-896.

80. Acar, G.; Idiman, F.; Idiman, E.; Kirkali, G.; Cakmakci, H.; Ozakbas, S. Nitric oxide as an activity marker in multiple sclerosis. *J. Neurol.* **2003**, *250(5)*, 588-592.

81. Danilov, A.I.; Andersson, M.; Bavand, N.; Wiklund, N.P.; Olsson, T.; Brundin, L. Nitric oxide metabolite determinations reveal continuous inflammation in multiple sclerosis. *J. Neuroimmunol.* **2003**, *136(1-2)*, 112-118.

82. Svenningsson, A.; Petersson, A.S.; Andersen, O.; Hansson, GK. Nitric oxide metabolites in CSF of patients with MS are related to clinical disease course. *Neurology* **1999**, *53(8)*, 1880-1882.

83. Brundin, L.; Morcos, E.; Olsson, T.; Wiklund, N.P.; Andersson, M. Increased intrathecal nitric oxide formation in multiple sclerosis; cerebrospinal fluid nitrite as activity marker. *Eur. J. Neurol.* **1999**, *6(5)*, 585-590.

84. Xue, Q.; Yan, Y.; Zhang, R.; Xiong, H. Regulation of iNOS on Immune Cells and Its Role in Diseases. *Int. J. Mol. Sci.* **2018**, *19*, 3805.

85. Fernando, V.; Zheng, X.; Walia, Y.; Sharma, V.; Letson, J.; Furuta, S. S-Nitrosylation: An Emerging Paradigm of Redox Signaling. *Antioxidants* **2019**, *8*, 404.

86. Pérez-Torres, I.; Manzano-Pech, L.; Rubio-Ruíz, M.E.; Soto, M.E.; Guarner-Lans, V. Nitrosative Stress and Its Association with Cardiometabolic Disorders. *Molecules* **2020**, *25*, 2555.

87. Bryll, A.; Skrzypek, J.; Krzyściak, W.; Szelągowska, M.; Śmierciak, N.; Kozicz, T.; Popiela, T. Oxidative-Antioxidant Imbalance and Impaired Glucose Metabolism in Schizophrenia. *Biomolecules* **2020**, *10*, 384.

88. Zhang, X.; Zhang, D.; Sun, W.; Wang, T. The Adaptive Mechanism of Plants to Iron Deficiency via Iron Uptake, Transport, and Homeostasis. *Int. J. Mol. Sci.* **2019**, *20*, 2424.

89. Venditti, P.; Di Meo, S. The Role of Reactive Oxygen Species in the Life Cycle of the Mitochondrion. *Int. J. Mol. Sci.* **2020**, *21*, 2173.

921    90.  López-Gambero, A.J.; Sanjuan, C.; Serrano-Castro, P.J.; Suárez, J.; Rodríguez de Fonseca, F. The
922         Biomedical Uses of Inositols: A Nutraceutical Approach to Metabolic Dysfunction in Aging and
923         Neurodegenerative Diseases. *Biomedicines* **2020**, *8*, 295.

924    91.  Gliozzi, M.; Scicchitano, M.; Bosco, F.; Musolino, V.; Carresi, C.; Scarano, F.; Maiuolo, J.; Nucera,
925         S.; Maretta, A.; Paone, S.; Mollace, R.; Ruga, S.; Zito, M.C.; Macrì, R.; Oppedisano, F.; Palma, E.;
926         Salvemini, D.; Muscoli, C.; Mollace, V. Modulation of Nitric Oxide Synthases by Oxidized LDLs:
927         Role in Vascular Inflammation and Atherosclerosis Development. *Int. J. Mol. Sci.* **2019**, *20*, 3294.

928    92.  Lopez-Moratalla, N; Gonzalez, A.; Aymerich, M.S.; López-Zabalza, M.J.; Pío, R.; de Castro, P.;
929         Santiago E. Monocyte inducible nitric oxide synthase in multiple sclerosis: regulatory role of
930         nitric oxide. *Nitric Oxide* **1997**, *1(1)*, 95-104.

931    93.  Calabrese, V.; Scapagnini, G.; Ravagna, A.; Bella, R.; Foresti, R.;   Bates, T.E.; Giuffrida
932         Stella, A.M.; Pennisi, G. Nitric oxide synthase is present in the cerebrospinal fluid of patients
933         with active multiple sclerosis and is associated with increases in cerebrospinal fluid protein
934         nitrotyrosine and S-nitrosothiols and with changes in glutathione levels. *J. Neurosci. Res.* **2002**,
935         *70(4)*, 580-587.

936    94.  Giles, G.I.; Nasim, M.J.; Ali, W.; Jacob, C. The Reactive Sulfur Species Concept: 15 Years
937         On. *Antioxidants* **2017**, *6*, 38.

938    95.  Schöneich, C. Thiyl Radical Reactions in the Chemical Degradation of Pharmaceutical
939         Proteins. *Molecules* **2019**, *24*, 4357.

940    96.  Ramírez, R.E.; García-Martínez, C.; Méndez, F. Understanding the Nucleophilic Character and
941         Stability of the Carbanions and Alkoxides of 1-(9-Anthryl)ethanol and Derivatives. *Molecules*
942         **2013**, *18*, 10254-10265.

943    97.  Bjørklund, G.; Crisponi, G.; Nurchi, V.M.; Cappai, R.; Buha Djordjevic, A.; Aaseth, J. A Review
944         on Coordination Properties of Thiol-Containing Chelating Agents Towards Mercury, Cadmium,
945         and Lead. *Molecules* **2019**, *24*, 3247.

946    98.  Głowacka, U.; Brzozowski, T.; Magierowski, M. Synergisms, Discrepancies and Interactions
947         between Hydrogen Sulfide and Carbon Monoxide in the Gastrointestinal and Digestive System
948         Physiology, Pathophysiology and Pharmacology. *Biomolecules* **2020**, *10*, 445.

949    99.  Benchoam, D.; Cuevasanta, E.; Möller, M.N.; Alvarez, B. Hydrogen Sulfide and Persulfides
950         Oxidation by Biologically Relevant Oxidizing Species. *Antioxidants* **2019**, *8*, 48.

951    100. McBean, G.J. Cysteine, Glutathione, and Thiol Redox Balance in Astrocytes. *Antioxidants* **2017**, *6*,
952         62.

953    101. Marozkina, N.; Gaston, B. An Update on Thiol Signaling: S-Nitrosothiols, Hydrogen Sulfide and
954         a Putative Role for Thionitrous Acid. *Antioxidants* **2020**, *9*, 225.

955    102. McNeil, N.M.R.; McDonnell, C.; Hambrook, M.; Back, T.G. Oxidation of Disulfides to
956         Thiolsulfinates with Hydrogen Peroxide and a Cyclic Seleninate Ester Catalyst. *Molecules*
957         **2015**, *20*, 10748-10762.

958    103. Grman, M.; Nasim, M.J.; Leontiev, R.; Misak, A.; Jakusova, V.; Ondrias, K.; Jacob, C. Inorganic
959         Reactive Sulfur-Nitrogen Species: Intricate Release Mechanisms or Cacophony in Yellow, Blue
960         and Red? *Antioxidants* **2017**, *6*, 14.

961    104. Nagahara, N.; Wróbel, M. $H_2S$, Polysulfides, and Enzymes: Physiological and Pathological
962         Aspects. *Biomolecules* **2020**, *10*, 640.

963    105. Kolluru, G.K.; Shen, X.; Kevil, C.G. Reactive Sulfur Species: A New Redox Player in
964         Cardiovascular Pathophysiology. *Arterioscler. Thromb. Vasc. Biol.* **2020**, *40(4)*, 874-884.

965    106. Bild, W.; Ciobica, A.; Padurariu, M.; Bild, V. The interdependence of the reactive species of
966         oxygen, nitrogen, and carbon. *J. Physiol. Biochem.* **2013**, *69(1)*, 147-154.

967    107. Monti, D A.; Zabrecky, G.; Leist, T.P.; Wintering, N.; Bazzan, A.J.; Zhan, T. Newberg, A.B. N-
968         acetyl Cysteine Administration Is Associated With Increased Cerebral Glucose Metabolism in
969         Patients With Multiple Sclerosis: An Exploratory Study. *Front. Neurol.* **2020**, *11*, 88.

970    108. Krysko, K.; Bischof, A.; Nourbakhsh, B.; Henry, R.; Revirajan, N.; Manguinao, M.; Li, Y.;
971         Waubant, E. N-acetyl cysteine for fatigue in progressive multiple sclerosis: A pilot randomized
972         double-blind placebo-controlled trial (P5.2-093). *Neurology* **2019**, *92* (15 Supplement).

109. Singhal, N.K.; Freeman, E.; Arning, E.; Wasek, B.; Clements, R.; Sheppard, C.; Blake, P. Bottiglieri, T.; McDonough, J. Dysregulation of methionine metabolism in multiple sclerosis. *Neurochem. Int.* **2018**, *112*, 1-4.

110. Mir F, et al "Methionine metabolism is altered in multiple sclerosis" SfN 2017; Abstract 475.16/N2; (Available online: https://www.medpagetoday.com/meetingcoverage/sfn/69274. 24 June 2020).

111. Roy, D; Chen, J.; Mamane, V. Methionine Metabolism Shapes T Helper Cell Responses through Regulation of Epigenetic Reprogramming. *Cell Metabolism* **2020**, *31(2)*, 250-266.

112. Ferreira, B.; Mendes, F.; Osório, N.; Caseiro, A.; Gabriel, A.; Valado, A. Glutathione in multiple sclerosis. *Br. J. Biomed. Sci.* **2013**, *70(2)*, 75-79.

113. Karg, E.; Klivényi, P.; Németh, I.; Bencsik, K.; Pintér, S.; Vécsei L. Nonenzymatic antioxidants of blood in multiple sclerosis. *J. Neurol.* **1999**, *246(7)*, 533-539.

114. Fominykh, V.; Onufriev, M.V.; Vorobyeva, A.; Brylev, L.; Yakovlev, A.A.; Zakharova, M.N.; Gulyaeva, N.V. Increased S-nitrosothiols are associated with spinal cord injury in multiple sclerosis. *J. Clin. Neurosci.* **2016**, *28*, 38-42.

115. Antognelli, C.; Perrelli, A.; Armeni, T.; Nicola Talesa, V.; Retta, S.F. Dicarbonyl Stress and S-Glutathionylation in Cerebrovascular Diseases: A Focus on Cerebral Cavernous Malformations. *Antioxidants* **2020**, *9*, 124.

116. Hwang, S.W.; Lee, Y.-M.; Aldini, G.; Yeum, K.-J. Targeting Reactive Carbonyl Species with Natural Sequestering Agents. *Molecules* **2016**, *21*, 280.

117. Pérez-Pérez, A.; Sánchez-Jiménez, F.; Vilariño-García, T.; Sánchez-Margalet, V. Role of Leptin in Inflammation and Vice Versa. *Int. J. Mol. Sci.* **2020**, *21*, 5887.

118. Khan, A.A.; Alsahli, M.A.; Rahmani, A.H. Myeloperoxidase as an Active Disease Biomarker: Recent Biochemical and Pathological Perspectives. *Med. Sci.* **2018**, *6*, 33.

119. Mannino, M.H.; Patel, R.S.; Eccardt, A.M.; Janowiak, B.E.; Wood, D.C.; He, F.; Fisher, J.S. Reversible Oxidative Modifications in Myoglobin and Functional Implications. *Antioxidants* **2020**, *9*, 549.

120. Gonos, E.S.; Kapetanou, M.; Sereikaite, J.; Bartosz, G.; Naparło, K.; Grzesik, M.; Sadowska-Bartosz, I. Origin and pathophysiology of protein carbonylation, nitration and chlorination in age-related brain diseases and aging. *Aging (Albany NY)* **2018**, *10(5)*, 868-901.

121. Mostert, J.P.; Ramsaransing, G.S.; Heersema, D.J.; Heerings, M.; Wilczak, N.; De Keyser, J. Serum uric acid levels and leukocyte nitric oxide production in multiple sclerosis patients outside relapses. *J. Neurol. Sci.* **2005**, *231(1-2)*, 41-44.

122. Minohara, M.; Matsuoka, T.; Li, W.; Osoegawa, M.; Ishizu, T.; Ohyagi, Y.; Kira, J. Upregulation of myeloperoxidase in patients with opticospinal multiple sclerosis: positive correlation with disease severity. *J. Neuroimmunol.* **2006**, *178(1-2)*, 156-160.

123. Tasset, I.; Aguera, E.; Sanchez-Lopez, F.; Feijóo, M.; Giraldo, A.I.; Cruz, A.H.; Gascón, Félix.; Túnez, I. Peripheral oxidative stress in relapsing remitting multiple sclerosis. *Clin. Biochem*. **2012**, *45(6)*, 440-444.

124. Cupp-Sutton, K.A.; Ashby, M.T. Biological Chemistry of Hydrogen Selenide. *Antioxidants* **2016**, *5*, 42.

125. Misra, S.; Boylan, M.; Selvam, A.; Spallholz, J.E.; Björnstedt, M. Redox-Active Selenium Compounds—From Toxicity and Cell Death to Cancer Treatment. *Nutrients* **2015**, *7*, 3536-3556.

126. Zoidis, E.; Seremelis, I.; Kontopoulos, N.; Danezis, G.P. Selenium-Dependent Antioxidant Enzymes: Actions and Properties of Selenoproteins. *Antioxidants* **2018**, *7*, 66.

127. Socha, K.; Kochanowicz, J.; Karpińska, E.; Soroczyńska, J.; Jakoniuk, M.; Mariak, Z.; Borawska, M.H. Dietary habits and selenium, glutathione peroxidase and total antioxidant status in the serum of patients with relapsing-remitting multiple sclerosis. *Nutr. J.* **2014**, *13*, 62.

128. Grandi, C.; D'Ovidio, M.C. Balance between Health Risks and Benefits for Outdoor Workers Exposed to Solar Radiation: An Overview on the Role of Near Infrared Radiation Alone and in Combination with Other Solar Spectral Bands. *Int. J. Environ. Res. Public Health* **2020**, *17(4)*, 1357.

129. Karimi, A.; Bahrampour, K.; Momeni Moghaddam, M.A.; Asadikaram, G.; Ebrahimi, G.; Torkzadeh-Mahani, M.; Esmaeili Tarzi, M.; Nematollahi, M.H. Evaluation of lithium serum level in multiple sclerosis patients: A neuroprotective element. *Mult. Scler. Relat. Disord.* **2017**, 17, 244-248.

130. Juybari, K.B.; Ebrahimi, G.; Momeni Moghaddam, M.A.; Asadikaram, G.; Torkzadeh-Mahani, M.; Akbari, M.; Mirzamohammadi, S.; Karimi, A.; Nematollahi, M.H. Evaluation of serum arsenic and its effects on antioxidant alterations in relapsing-remitting multiple sclerosis patients. *Mult. Scler. Relat. Disord.* **2018**, *19*, 79-84.

131. Carroll, L.D.; Davies, M.J. Reaction of Selenium Compounds with Oxygen Species and the Control of Oxidative Stress. In *Organoselenium Compounds in Biology and Medicine: Synthesis, Biological and Therapeutic Treatments*. Eds: Jain, V.K.; Priyadarsini, K.I., Eds; Royal Society of Chemistry; United Kingdom; 2018; pp. 254-275.

132. Xiao, W.; Loscalzo, J. Metabolic Responses to Reductive Stress. *Antioxid. Redox Signal* **2020**, *32(18)*, 1330-1347.

133. Korge, P.; Calmettes, G.; Weiss, .JN. Increased reactive oxygen species production during reductive stress: The roles of mitochondrial glutathione and thioredoxin reductases. *Biochim. Biophys. Acta* **2015**, *1847(6-7)*, 514-525.

134. Bradshaw, P.C. Cytoplasmic and Mitochondrial NADPH-Coupled Redox Systems in the Regulation of Aging. *Nutrients* **2019**, *11(3)*, 504.

135. Pérez-Torres, I.; Guarner-Lans, V.; Rubio-Ruiz, M.E. Reductive Stress in Inflammation-Associated Diseases and the Pro-Oxidant Effect of Antioxidant Agents. *Int. J. Mol. Sci.* **2017**, *18*, 2098.

136. Jozefczak, M.; Remans, T.; Vangronsveld, J.; Cuypers, A. Glutathione Is a Key Player in Metal-Induced Oxidative Stress Defenses. *Int. J. Mol. Sci.* **2012**, *13*, 3145-3175

137. Singhal, S.S.; Singh, S.P.; Singhal, P.; Horne, D.; Singhal, J.; Awasthi, S. Antioxidant Role of Glutathione S-Transferases: 4-Hydroxynonenal, a Key Molecule in Stress-Mediated Signaling. *Toxicol. Appl. Pharmacol.* **2015**, *289(3)*, 361–370.

138. Bocedi, A.; Noce, A.; Marrone, G.; Noce, G.; Cattani, G.; Gambardella, G.; Di Lauro, M.; Di Daniele, N.; Ricci, G. Glutathione Transferase P1-1 an Enzyme Useful in Biomedicine and as Biomarker in Clinical Practice and in Environmental Pollution. *Nutrients* **2019**, *11*, 1741.

139. Shukla, V.K.; Jensen, G.E.; Clausen, J. Erythrocyte glutathione perioxidase deficiency in multiple sclerosis. *Acta Neurol. Scand.*, **1977**, *56(6)*, 542-550.

140. Szeinberg, A.; Golan, R.; Ben Ezzer, J.; Sarova-Pinhas, I.; Sadeh, M.; Braham, J. Decreased erythrocyte glutathione peroxidase activity in multiple sclerosis. *Acta Neurol. Scand.* **1979**, *60(5)*, 265-271.

141. Szeinberg, A.; Golan, R.; Ben-Ezzer, J.; Sarova-Pinhas, I.; Kindler, D. Glutathione peroxidase activity in various types of blood cells in multiple sclerosis. *Acta Neurol. Scand.* **1981**, *63(1)*, 67-75.

142. Ljubisavljevic, S.; Stojanovic, I.; Cvetkovic, T.; Vojinovic, S.; Stojanov, D.; Stojanovic, D.; Bojanic, V.; Stokanovic, D.; Pavlovic, D. Glutathione homeostasis disruption of erythrocytes, but not glutathione peroxidase activity change, is closely accompanied with neurological and radiological scoring of acute CNS inflammation. *Neuroimmunomodulation* **2014**, *21(1)*, 13-20.

143. Zachara, B.; Gromadzinska, J.; Czernicki, J.; Maciejek, Z.; Chmielewski, H. Red blood cell glutathione peroxidase activity in multiple sclerosis. *Klin. Wochenschr.*, **1984**, *62(4)*, 179-182.

144. Calabrese, V.; Raffaele, R.; Cosentino, E.; Rizza, V. Changes in cerebrospinal fluid levels of malondialdehyde and glutathione reductase activity in multiple sclerosis. *Int. J. Clin. Pharmacol. Res.* **1994**, *14(4)*, 119-123.

145. Jensen, G.E.; Gissel-Nielsen, G.; Clausen, J. Leucocyte glutathione peroxidase activity and selenium level in multiple sclerosis. *J. Neurol. Sci.* **1980**, *48(1)*, 61-67.

146. Reiter, R.J.; Tan, D.X.; Rosales-Corral, S.; Galano, A.; Zhou, X.J.; Xu, B. Mitochondria: Central Organelles for Melatonin's Antioxidant and Anti-Aging Actions. *Molecules* **2018**, *23*, 509.

147. Jensen, G.E. Clausen, J. Glutathione peroxidase and reductase, glucose-6-phosphate dehydrogenase and catalase activities in multiple sclerosis. *J. Neurol. Sci.* **1984**, *63(1)*, 45-53.

148. Ljubisavljevic, S.; Stojanovic, I.; Vojinovic, S.; Stojanov, D.; Stojanovic, S.; Kocic, G.; Savic, D.; Cvetkovic, T.; Pavlovic, D. Cerebrospinal fluid and plasma oxidative stress biomarkers in different clinical phenotypes of neuroinflammatory acute attacks. Conceptual accession: from fundamental to clinic. *Cell Mol. Neurobiol.* **2013**, *33(6)*, 767-777.

149. Belcastro, E.; Gaucher, C.; Corti, A.; Leroy, P.; Lartaud, I.; Pompella, A. Regulation of Protein Function by S-nitrosation and S-glutathionylation: Processes and Targets in Cardiovascular Pathophysiology. *Biol. Chem.* **2017**, *398(12)*, 1267-1293.

150. Mahmoudian, E.; Khalilnezhad, A.; Gharagozli, K.; Amani, D. Thioredoxin-1, redox factor-1 and thioredoxin-interacting protein, mRNAs are differentially expressed in Multiple Sclerosis patients exposed and non-exposed to interferon and immunosuppressive treatments. *Gene* **2017**, *634*, 29-36.

151. Voigt, D.; Scheidt, U.; Derfuss, T.; Brück, W.; Junker, A. Expression of the Antioxidative Enzyme Peroxiredoxin 2 in Multiple Sclerosis Lesions in Relation to Inflammation. *Int. J. Mol. Sci.* **2017**, *18*, 760.

152. Todisco, S.; Convertini, P.; Iacobazzi, V.; Infantino, V. TCA Cycle Rewiring as Emerging Metabolic Signature of Hepatocellular Carcinoma. *Cancers* **2020**, *12*, 68.

153. Schaur, R.J.; Siems, W.; Bresgen, N.; Eckl, P.M. 4-Hydroxy-nonenal—A Bioactive Lipid Peroxidation Product. *Biomolecules* **2015**, *5*, 2247-2337.

154. McArdle, B.; Mackenzie, I.C.; Webster, G.R. STUDIES ON INTERMEDIATE CARBOHYDRATE METABOLISM IN MULTIPLE SCLEROSIS. *J. Neurol. Neurosurg. Psychiatry*, **1960**, *23(2)*, 127-132.

155. Nijland, P.G.; Molenaar, R.J.; van der Pol, S.M.; van der Valk, P.; van Noorden, C.J.; de Vries, H.E.; van Horssen, J. Differential expression of glucose-metabolizing enzymes in multiple sclerosis lesions. *Acta Neuropathol. Commun.* **2015**, *3*, 79.

156. Hirsch, H.E.; Blanco, C.E. Parks, M.E. Glycerol phosphate dehydrogenase: reduced activity in multiple sclerosis plaques confirms localization in oligodendrocytes. *J. Neurochem.* **1980**, *34(3)*, 760-762.

157. Cores, Á.; Piquero, M.; Villacampa, M.; León, R.; Menéndez, J.C. NRF2 Regulation Processes as a Source of Potential Drug Targets against Neurodegenerative Diseases. *Biomolecules* **2020**, *10*, 904.

158. Orrù, C.; Perra, A.; Kowalik, M.A.; Rizzolio, S.; Puliga, E.; Cabras, L.; Giordano, S.; Columbano, A. Distinct Mechanisms Are Responsible for Nrf2-Keap1 Pathway Activation at Different Stages of Rat Hepatocarcinogenesis. *Cancers* **2020**, *12*, 2305.

159. Lamichane, S.; Dahal Lamichane, B.; Kwon, S.-M. Pivotal Roles of Peroxisome Proliferator-Activated Receptors (PPARs) and Their Signal Cascade for Cellular and Whole-Body Energy Homeostasis. *Int. J. Mol. Sci.* **2018**, *19*, 949.

160. Xi, Y.; Zhang, Y.; Zhu, S.; Luo, Y.; Xu, P.; Huang, Z. PPAR-Mediated Toxicology and Applied Pharmacology. *Cells* **2020**, *9*, 352.

161. Vargas-Mendoza, N.; Morales-González, Á.; Madrigal-Santillán, E.O.; Madrigal-Bujaidar, E.; Álvarez-González, I.; García-Melo, L.F.; Anguiano-Robledo, L.; Fregoso-Aguilar, T.; Morales-Gonzalez, J.A. Antioxidant and Adaptative Response Mediated by Nrf2 during Physical Exercise. *Antioxidants (Basel)* **2019**, *8(6)*, 196.

162. Ferret-Sena, V.; Capela, C.; Sena, A. Metabolic Dysfunction and Peroxisome Proliferator-Activated Receptors (PPAR) in Multiple Sclerosis. *Int. J. Mol. Sci.* **2018**, *19*, 1639.

163. Witte, M.E.; Nijland, P.G.; Drexhage, J.A.; Gerritsen, W.; Geerts, D.; van Het Hof, B.; Reijerkerk, A.; de Vries, H.E.; van der Valk, P.; van Horssen, J. Reduced expression of PGC-1α partly underlies mitochondrial changes and correlates with neuronal loss in multiple sclerosis cortex. *Acta Neuropathol*. **2013**, *125(2)*, 231-243.

164. Del Bo', C.; Bernardi, S.; Marino, M.; Porrini, M.; Tucci, M.; Guglielmetti, S.; Cherubini, A.; Carrieri, B.; Kirkup, B.; Kroon, P.; Zamora-Ros, R.; Hidalgo Liberona, N.; Andres-Lacueva, C.; Riso, P. Systematic Review on Polyphenol Intake and Health Outcomes: Is there Sufficient

1127  Evidence to Define a Health-Promoting Polyphenol-Rich Dietary Pattern? *Nutrients* **2019**, *11*,
1128  1355.

1129  165. Shenkin, A. Micronutrients in health and disease. *Postgrad. Med. J.* **2006**, *82(971)*, 559–567.

1130  166. Peris, E.; Micallef, Peter.; Paul, A.; Palsdottir, V.; Enejder, A.; Bauzá-Thorbrügge, M.; Olofsson,
1131  C.S.; Asterholm, W.I. Antioxidant treatment induces reductive stress associated with
1132  mitochondrial dysfunction in adipocyte. *J. Biol. Chem.* **2019**, *294(7)*, 2340–2352.

1133  167. Feige, J.; Moser, T.; Bieler, L.; Schwenker, K.; Hauer, L.; Sellner, J. Vitamin D Supplementation
1134  in Multiple Sclerosis: A Critical Analysis of Potentials and Threats. *Nutrients*, **2020**, *12*, 783.

1135  168. Oliveira, S.R.; Kallaur, A.P.; Simão, A.N.; Morimoto, H.K.; Lopes, J.; Panis, C.; Petenucci, D.L.;
1136  da Silva, E.; Cecchini, R.; Kaimen-Maciel, D.R.; Reiche, E.M. Oxidative stress in multiple sclerosis
1137  patients in clinical remission: association with the expanded disability status scale. *J. Neurol. Sci.*
1138  **2012**, *321(1-2)*, 49-53.

1139  169. Miller, E.; Walczak, A.; Saluk, J.; Ponczek, M.B.; Majsterek, I. Oxidative modification of patient's
1140  plasma proteins and its role in pathogenesis of multiple sclerosis. *Clin. Biochem*. **2012**, *45(1-2)*, 26-
1141  30.

1142  170. Sadowska-Bartosz, I.; Adamczyk-Sowa, M.; Gajewska, A.; Bartosz, G. Oxidative modification of
1143  blood serum proteins in multiple sclerosis after interferon or mitoxantrone treatment. *J.*
1144  *Neuroimmunol.* **2014**, *266(1-2)*, 7-74.

1145  171. Morel, A.; Bijak, M.; Niwald, M.; Miller, E.; Saluk, J. Markers of oxidative/nitrative damage of
1146  plasma proteins correlated with EDSS and BDI scores in patients with secondary progressive
1147  multiple sclerosis. *Redox Rep.* **2017**, *22(6)*, 547-555.

1148  172. Adamczyk-Sowa, M.; Galiniak, S.; Żyracka, E.; Grzesik, M.; Naparło, K.; Sowa, P.; Bartosz, G.;
1149  Sadowska-Bartosz, I. Oxidative Modification of Blood Serum Proteins in Multiple Sclerosis after
1150  Interferon Beta and Melatonin Treatment. *Oxid. Med. Cell Longev.* **2017**, *2017*, 7905148.

1151  173. Rommer, P.S.; Greilberger, J.; Salhofer-Polanyi, S.; Auff, E.; Leutmezer, F. Herwig, R. Elevated
1152  levels of carbonyl proteins in cerebrospinal fluid of patients with neurodegenerative diseases.
1153  *Tohoku J. Exp. Med.* **2014**, *234(4)*, 313-317.

1154  174. Irani, D.N. Cerebrospinal fluid protein carbonylation identifies oxidative damage in
1155  autoimmune demyelination. *Ann. Clin. Transl. Neurol.* **2016**, *4(2)*, 145-150.

1156  175. Teixeira, D.; Fernandes, R.; Prudêncio, C.; Vieira, M. 3-Nitrotyrosine quantification methods:
1157  Current concepts and future challenges. *Biochimie* **2016**, *125*, 1-11.

1158  176. Zabaleta, M.; Marino, R.; Borges, J. Camargo, B.; Ordaz, P.; De Sanctis, J.B.; Bianco, N.E. Activity
1159  profile in multiple sclerosis: an integrative approach. A preliminary report. *Mult. Scler.* **2002**,
1160  *8(4)*, 343-349.

1161  177. Iarlori, C.; Gambi, D.; Lugaresi, A.; Patruno, A.; Felaco, M.; Salvatore, M.; Speranza, L.; Reale,
1162  M. Reduction of free radicals in multiple sclerosis: effect of glatiramer acetate (Copaxone). *Mult.*
1163  *Scler*. **2008**, *14(6)*, 739-748.

1164  178. Seven, A.; Aslan, M.; Incir, S.; Altintas, A. Evaluation of oxidative and nitrosative stress in
1165  relapsing remitting multiple sclerosis: effect of corticosteroid therapy. *Folia Neuropathol.* **2013**,
1166  *51(1)*, 58-64.

1167  179. Stojanovic, I.; Vojinovic, S.; Ljubisavljevic, S.; Pavlovic, R.; Basic, J.; Pavlovic, D.; Ilic, A.;
1168  Cvetkovic, T.; Stukalov, M. INF-β1b therapy modulates L-arginine and nitric oxide metabolism
1169  in patients with relapse remittent multiple sclerosis. *J. Neurol. Sci.* **2012**, *323(1-2)*, 187-192.

1170  180. Poerschke, R.L.; Fritz, K.S.; Franklin, C.C. Methods to detect protein glutathionylation. *Curr.*
1171  *Protoc. Toxicol.* **2013**, *57*, 6.17.1-6.17.18.

1172  181. Srivastava, D.; Kukkuta Sarma, G.R.; Dsouza, D.S.; Muralidharan, M.; Srinivasan, K.; Mandal,
1173  A.K. Characterization of residue-specific glutathionylation of CSF proteins in multiple sclerosis
1174  - A MS-based approach. *Anal Biochem.* **2019**, *564-565*, 108-115.

1175  182. Garibaldi, S.; Barisione, C.; Marengo, B.; Ameri, P.; Brunelli, C.; Balbi, M.; Ghigliotti, G.
1176  Advanced Oxidation Protein Products-Modified Albumin Induces Differentiation of RAW264.7
1177  Macrophages into Dendritic-Like Cells Which Is Modulated by Cell Surface Thiols. *Toxins (Basel)*
1178  **2017**, *9(1)*, 27.

32 of 33

183. Hányšová, S.; Čierny, D.; Petráš, M.; Lehotský, J. Elevated plasma levels of advanced oxidation protein products in Slovak multiple sclerosis patients: possible association with different disability states. *Act Nerv. Super Rediviva.* **2017**, *59(2)*, 45–50.

184. Gill, V.; Kumar, V.; Singh, K.; Kumar, A.; Kim, J.-J. Advanced Glycation End Products (AGEs) May Be a Striking Link Between Modern Diet and Health. *Biomolecules* **2019**, *9*, 888.

185. Wetzels, S.; Vanmierlo, T.; Scheijen, J.L.J.M.; van Horssen, J.; Amor, S.; Somers, V.; Schalkwijk, C.G.; Hendriks, J.J.A.; Wouters, K. Methylglyoxal-Derived Advanced Glycation Endproducts Accumulate in Multiple Sclerosis Lesions. *Front. Immunol.* **2019**, *10*, 855.

186. Tain, Y.; Hsu, C. Toxic Dimethylarginines: Asymmetric Dimethylarginine (ADMA) and Symmetric Dimethylarginine (SDMA). *Toxins*, **2017**, *9*, 92.

187. Haghikia, A.; Kayacelebi, A.A., Beckmann, B.; Hanff, E.; Gold, R.; Haghikia, A.; Tsikas, D. Serum and cerebrospinal fluid concentrations of homoarginine, arginine, asymmetric and symmetric dimethylarginine, nitrite and nitrate in patients with multiple sclerosis and neuromyelitis optica. *Amino Acids* **2015**, *47(9)*, 1837-1845.

188. Zarkovic, N. Antioxidants and Second Messengers of Free Radicals. *Antioxidants* **2018**, *7*, 158.

189. Ito, F.; Sono, Y.; Ito, T. Measurement and Clinical Significance of Lipid Peroxidation as a Biomarker of Oxidative Stress: Oxidative Stress in Diabetes, Atherosclerosis, and Chronic Inflammation. *Antioxidants (Basel)*, **2019**, *8(3)*, 72.

190. Teunissen, C.E.; Sombekke, M.; van Winsen, L.; Killestein, J.; Barkhof, F.; Polman, C.H.; Dijkstra, C.D.; Blankenstein, M.A.; Pratico, D. Increased plasma 8,12-iso-iPF2alpha- VI levels in relapsing multiple sclerosis patients are not predictive of disease progression. *Mult. Scler.* **2012**, *18(8)*, 1092-1098.

191. Miller, E.; Mrowicka, M.; Saluk-Juszczak, J.; Ireneusz, M. The level of isoprostanes as a non-invasive marker for in vivo lipid peroxidation in secondary progressive multiple sclerosis. *Neurochem. Res.* **2011**, *36(6)*, 1012-1016.

192. Gonzalo, H.; Brieva, L.; Tatzber, F.; Jové, M.; Cacabelos, D.; Cassanyé, A.; Lanau-Angulo, L.; Boada, J.; Serrano, J.C.; González, C.; Hernández, L.; Peralta, S.; Pamplona, R.; Portero-Otin, M. Lipidome analysis in multiple sclerosis reveals protein lipoxidative damage as a potential pathogenic mechanism. *J. Neurochem.* **2012**, *123(4)*, 622-634.

193. Greco, A.; Minghetti, L.; Sette, G.; Fieschi, C.; Levi, G. Cerebrospinal fluid isoprostane shows oxidative stress in patients with multiple sclerosis. *Neurology* **1999**, *53(8)*, 1876-1879.

194. Pohl, E.E.; Jovanovic, O. The Role of Phosphatidylethanolamine Adducts in Modification of the Activity of Membrane Proteins under Oxidative Stress. *Molecules* **2019**, *24*, 4545.

195. Ghabaee, M.; Jabedari, B.;, Al-E-Eshagh, N.; Ghaffarpour, M.; Asadi, F. Serum and cerebrospinal fluid antioxidant activity and lipid peroxidation in Guillain-Barre syndrome and multiple sclerosis patients. *Int. J. Neurosci.* **2010**, *120(4)*, 301-304.

196. Pawlowski, J.; Shukla, P.; Bielekova, B. Identifying CSF Biomarkers of Oxidative Stress in Patients with Multiple Sclerosis. **2011**. DOI: 10.13140/RG.2.1.4335.2082. Available online: https://www.researchgate.net/publication/290998239_Identifying_CSF_Biomarkers_of_Oxidative_Stress_in_Patients_with_Multiple_Sclerosis (28 August 2020)

197. Villoslada, P.; Alonso, C.; Agirrezabal, I.; Kotelnikova, E.; Zubizarreta, I.; Pulido-Valdeolivas, I.; Saiz, A.; Comabella M.; Montalban, X.; Villar, L.; Alvarez-Cermeño, J.C.; Fernández, O.; Alvarez-Lafuente, R.; Arroyo, R.; Castro, A. Metabolomic signatures associated with disease severity in multiple sclerosis. *Neurol. Neuroimmunol. Neuroinflamm.* **2017**, *4(2)*, e321.

198. Håkansson, I.; Gouveia-Figueira, S.; Ernerudh, J.; Vrethem, M.; Ghafouri, N.; Ghafouri, B.; Nording, M. Oxylipins in cerebrospinal fluid in clinically isolated syndrome and relapsing remitting multiple sclerosis. Prostaglandins *Other Lipid Mediat.* **2018**, *138*, 41-47.

199. Fellows Maxwell, K.; Bhattacharya, S.; Bodziak, M.L.; Jakimovski, D.; Hagemeier, J.; Browne, R.W.; Weinstock-Guttman, B.; Zivadinov, R.; Ramanathan, M. Oxysterols and apolipoproteins in multiple sclerosis: a 5 year follow-up study. *J. Lipid Res.* **2019**, *60(7)*, 1190-1198.

200. Palavra, F.; Marado, D.; Mascarenhas-Melo, F.; Sereno, J.; Teixeira-Lemos, E.; Nunes, C.C.; Gonçalves, G.; Teixeira, F; Reis, F. New markers of early cardiovascular risk in multiple sclerosis patients: oxidized-LDL correlates with clinical staging. *Dis. Markers* **2013**, *34(5)*, 341-348.

201. Besler, H.T.; Comoğlu, S. Lipoprotein oxidation, plasma total antioxidant capacity and homocysteine level in patients with multiple sclerosis. *Nutr. Neurosci.* **2003**, *6(3)*, 189-196.

202. Salemi, G.; Gueli, M.C.; Vitale, F.; Battaglieri, F.; Guglielmini, E.; Ragonese, P.; Trentacosti, A.; Massenti, M.F.; Savettieri, G.; Bono, A. Blood lipids, homocysteine, stress factors, and vitamins in clinically stable multiple sclerosis patients. *Lipids Health Dis.* **2010**, *9*, 19.

203. Meyers, L.; Groover, C.J.; Douglas, J.; Lee, S.; Brand, D.; Levin, M.C. Gardner, L.A. A role for Apolipoprotein A-I in the pathogenesis of multiple sclerosis. *J. Neuroimmunol.* **2014**, *277(1-2)*, 176-185.

204. van de Kraats, C.; Killestein, J.; Popescu, V.; Rijkers, E.; Vrenken, H.; Lütjohann, D.; Barkhof, F.; Polman, C.H.; Teunissen, C.E. Oxysterols and cholesterol precursors correlate to magnetic resonance imaging measures of neurodegeneration in multiple sclerosis. *Mult. Scler.* **2014**, *20(4)*, 412-417.

205. Graille, M.; Wild, P.; Sauvain, J.-J.; Hemmendinger, M.; Guseva Canu, I.; Hopf, N.B. Urinary 8-OHdG as a Biomarker for Oxidative Stress: A Systematic Literature Review and Meta-Analysis. *Int. J. Mol. Sci.* **2020**, *21*, 3743.

206. Ibitoye, R.; Kemp, K.C.; Rice, C.; M. Hares, K.M., Scolding, N.J.; Wilkins, A. Oxidative stress-related biomarkers in multiple sclerosis: a review. *Biomark. Med.* **2016**, *10(8)*, 889-902.

207. Taguchi, Y.-H.; Wang, H. Exploring MicroRNA Biomarkers for Parkinson's Disease from mRNA Expression Profiles. *Cells* **2018**, *7*, 245.

208. Brito, L.M.; Ribeiro-dos-Santos, Â.; Vidal, A.F.; de Araújo, G.S., on behalf of the Alzheimer's Disease Neuroimaging Initiative; Differential Expression and miRNA–Gene Interactions in Early and Late Mild Cognitive Impairment. *Biology* **2020**, *9*, 251.

209. Catanesi, M.; d'Angelo, M.; Tupone, M.G.; Benedetti, E.; Giordano, A.; Castelli, V.; Cimini, A. MicroRNAs Dysregulation and Mitochondrial Dysfunction in Neurodegenerative Diseases. *Int. J. Mol. Sci.* **2020**, *21*, 5986.

210. Mohammed, E.M.A. Environmental Influencers, MicroRNA, and Multiple Sclerosis. *J. Cent. Nerv. Syst. Dis.* **2020**, *12*, 1179573519894955.

211. Martinez, B.; Peplow, P.V. MicroRNAs in blood and cerebrospinal fluid as diagnostic biomarkers of multiple sclerosis and to monitor disease progression. *Neural. Regen. Res.* **2020**, *15*, 606-619.

212. Pfaff, A.L.; Bubb, V.J.; Quinn, J.P.; Koks, S. An increased burden of highly active 3 retrotransposition competent L1s is associated with 4 Parkinson's disease risk and progression in the PPMI 5 cohort. *Int. J. Mol. Sci.* **2020** (submitted).

213. Geis, F.K.; Goff, S.P. Silencing and Transcriptional Regulation of Endogenous Retroviruses: An Overview. *Viruses* **2020**, *12*, 884.

214. Dhama, K.; Latheef, S.K.; Dadar, M.; Samad, H.A.; Munjal, A.; Khandia, R.; Karthik, K.; Tiwari, R.; Yatoo, M.I.; Bhatt, P.; Chakraborty, S.; Singh, K.P.; Iqbal, H.M.N.; Chaicumpa, W.; Joshi, S.K. Biomarkers in Stress Related Diseases/Disorders: Diagnostic, Prognostic, and Therapeutic Values. *Front. Mol. Biosci.* **2019**, *6*, 91.