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Chapter

Role of Lipid Peroxidation Process in Neurodegenerative Disorders

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Abstract

Lipid peroxidation is one of the primary events of the cell injury process. In pathophysiological condition, it is undergoing the initiation of organ damage. Various free radicals are playing a key role in this lipid peroxidation process. Free radical associated organ damage involves the three major phases, that is, initiation, propagation and termination. The primary source of various free radical formations is mediated through the pathophysiological function of mitochondria. Lipid peroxidation is contributed to the multiple neurodegenerative disorders. Thus, the various endogenous cellular anti-oxidant systems are regulated lipid peroxidation process and control the neurodegenerative action. Some of the molecules are targeted to attenuate the lipid peroxidation and their mediators for the prevention of neurodegeneration.

Keywords: malondialdehyde, vascular dementia, Alzheimer disease, multiple sclerosis

1. Introduction

Lipid peroxidation (LPO) is a complex process of the cellular system. The reactive oxygen species (ROS) such as superoxide anion, hydroxyl radical and hydrogen peroxide radicals play a key role in the process of lipid peroxidation [1]. Oxygen radicals, that is, superoxide anions are a primary bioactive molecule in LPO process. LPO process releases the various metabolic intermediated products such as malondialdehyde (MDA) and 4-hydroxynonenal (HNE) [2]. Further, the accumulation of LPO products; even it is small amounts induces the cell death process via multiple cell signaling process [3, 4]. ROS are ready to attack/interact with various bio molecules like polyunsaturated fatty acids (PUFA) of the fatty acid membrane. Then, LPO products are initiating the multiple self-propagative chain reactions [5]. This LPO associated destruction of membrane lipids and their intermediate/end-products are potentially dangerous for the various cells, tissues and organs. However, the LPO process is overcome by the cellular enzymatic system such as catalase (CAT) & superoxide dismutase (SOD); and non-enzymatic molecules like vitamins A and E [6]. Thus, lipid peroxidation is a self-propagating chain-reaction and involves the multiple ways of LPO product formation; so the availability of few lipid products can cause the significant tissue damage [7]. However, the extensive

research about the lipid peroxidation process and products are not yet been studied. The precise action and regulatory function of LPO in various pathophysiological conditions of neurodegenerative disorders such as Alzheimer disease (AD), dementia, Parkinson disease (PD), Huntington disease (HD), multiple sclerosis (MS), amylotropic lateral sclerosis (ALS), stroke and neuropathy are needed to be investigated [8, 9]. This book chapter is focused on the role of the lipid peroxidation process in neurodegenerative disorders.

2. Relationships of free radicals and LPO

LPO occurs due to the generation of free radicals process in the biological system. The free radicals are readily attacking the phospholipids of cell membrane leads to degrading the lipids action [10]. This rapid reaction towards lipid membrane is due to the availability of multiple double bonds between methylene (—CH_2—) bridges and reactive hydrogen atoms. This is most frequently occurs with polyunsaturated fatty acids (PUFA) [11]. The free radical reactions are self-perpetuating chain reactions and it is highly reactive molecules with a various biomolecule such as protein, lipids, mitochondria, endoplasmic reticulum and DNA due to its unpaired electrons [12]. In addition, these radicalsare existed very short duration, that is, 10^{-9}–10^{-12} second. However, before diverging of these free radicals are reacts with another molecule; to make their own stability by attracting or donate the electrons [13]. Generally, controlled generation of free radicals under normal body condition is good for the physiological process; because it enhances the immune cell activation and stimulates the various cellular systems.

Unfortunately, the large quantity of free radical generation causes the cell death. The abundant generation of free radicals is occurred due to abnormal metabolic and homeostatic functions. Normally the raising of free radicals is controlled by various endogenous anti-oxidant defense systems. There are two major factors are employing the activation of free radical associated lipid peroxidation process. The primary factor is increasing of cytosolic free radical concentration and it occurs due to enzymatic and mitochondrial mediated reactions [14]. Another factor is the reduction anti-oxidant fence system and it occurs due to the changes in the normal endogenous enzymatic pool. The imbalanced action of free radicals ate responsible for the LPO. LPO process not only occurs in cell membrane lipids; it also occurs in mitochondria, endoplasmic reticulum and nuclear membrane. This intracellular reaction of LPO is enhancing the cell death process [15]. Later stage of LPO process is also enhanced release of various biomolecules which activates the paracrine actions. The overall effect is procuring the organ and system failure. Here some of the examples are listed for the lipid peroxidation associated disorders such as cancer, atherosclerosis, myocardial infarction, coronary artery disease, liver failure, renal failure and autoimmune disease. In addition, the numerous reports are documented that, LPO process also enhances the pathogenesis of neurological disorders such as Alzheimer's disorder; Parkinson disease; multiple sclerosis, vascular dementia, stroke and neuropathic pain [16].

3. Molecular mechanism of free radicals, antioxidant and toxicity reactions

The free radical (R*) formation is mainly due to the abnormal bio-activation process sometimes due to xenobiotic reactions such as cytochrome P_{450}; prostaglandin synthase and lipoxygenase reactions. Free radical associated lipid peroxidation

reaction has three stages. (1) *Initiation stage*: in this stage, free radicals are attacking the covalently bonded molecules due to its high affinity [17]. The covalent bond containing bio-molecules are DNA, proteins, lipids and phospholipids. The membrane phospholipids, that is, PUFA is a primary target in the cellular system. In this stage fatty acid radical, that is, lipid radical (L*) is produced. (2) *Propagation stage*: the primary noticeable initiators of propagation stage of free radicals are reactive oxygen species (ROS; i.e., OH• and HOO•). This stage another lipid radicals, that is, lipid peroxy radical (LOO*) and lipid hydroperoxide (LOOH) are produced. Here, LOOH is non-radical. Whereas, when radicalsreact with non-radical molecules; non-radical molecules ready to changes their own property lead to form another active radical. This process is called as "chain reaction mechanism". (3) *Termination stage*: in this stage; different molecules are involved to speed up termination free radical—LPO reaction by neutralizing free radicals such agent is also called antioxidants such as vitamin E and vitamin C. Some of the anti-oxidants molecules are presents within the body like superoxide dismutase, catalase and glutathione peroxidase. These molecules are actively converting the LOO* and LOOH molecules to stable lipid alcohol (LOH). It is non-toxic to the biological system. Generally, the radical reaction stops when two radicals are reacted and produces the non-radical species. However, these reaction-sare happening, when the concentration of radical species is higher. In pathological conditions, the failure of the termination stage of LPO process leads to produce the multiple lipid peroxidative products [18–20]. The free radical (R*) associated lipid peroxidation in two different phases. The first phase is the lipid phase; it occurs in the cell membrane. The second phase is an aqueous phase; it occurs in the cytosolic region of the cell. Antioxidants are regulated inboth phases of the LPO process [21].

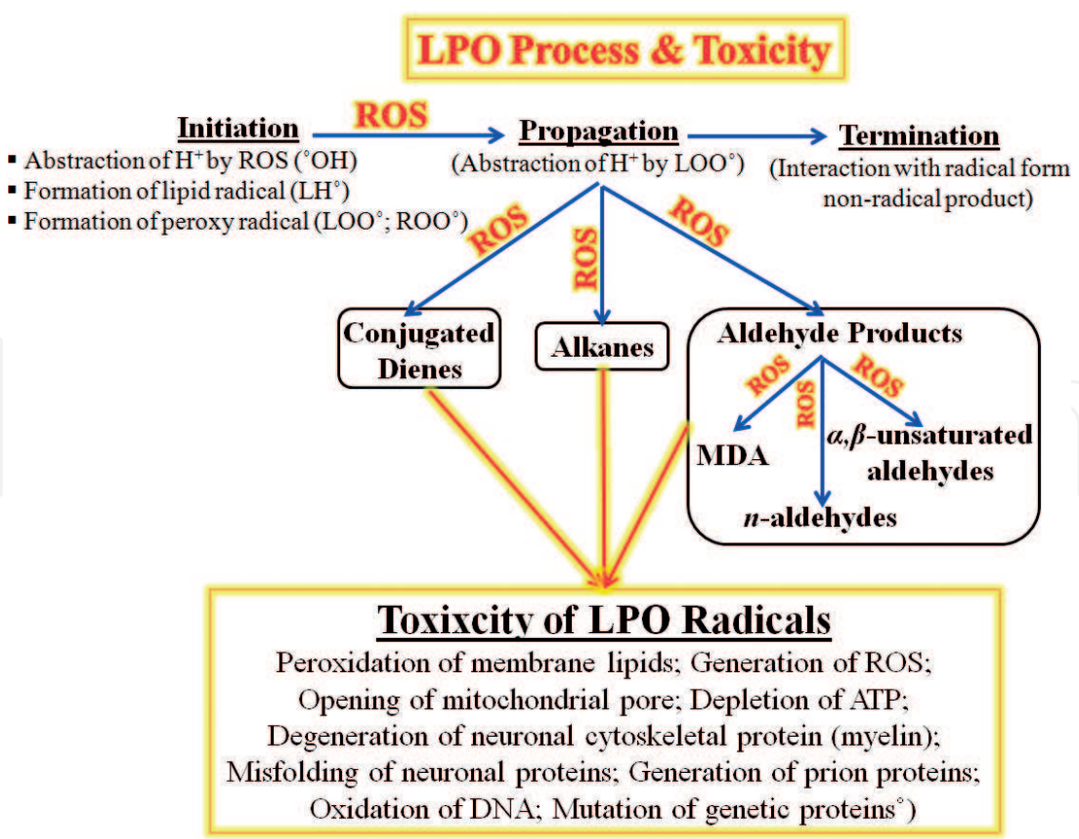

Figure 1.
This illustration is showing the reactions between free radicals, lipids and antioxidant molecules. Mechanism of LPO process and lipid radical associated neurotoxicity are undergoes the following actions, that is, initiation, propagation and termination. Whereas, the propagation stage of lipid radicals are induce the formation of various lipid radicals. Finally, it interacts with multiple levels of biomolecular changes leads to cause the neurodegeneration.

In lipid phase, PUFA methylene (—H—) bridges are converts to PUFA oxy (—OO*—) radical. An antioxidant such as tocopherol (Toc-OH) induces the PUFA oxy (—OO*—) radical conversion to PUFA oxy (—OOH—) molecule. PUFA peroxy (—OOH—) bridged molecule biologically non-toxic. Further nontoxic PUFA peroxy (—OOH—) bridged molecules are converted to PUFA peroxy (—OOH*—) molecule with the action of phospholipase A_2 (PLA_2). In this process is shifting the lipid phase to the aqueous phase of the reaction [22]. The PUFA peroxy (—OOH*—) molecules are toxic to the cellular system [23]. These molecules are regulated by two endogenous enzymatic anti-oxidant systems such as catalase and glutathione peroxidase. Catalase is directly converting the PUFA peroxy (—OOH*—) molecules to PUFA peroxy (—OH—) molecules. Glutathione peroxidase enhances the neutralizing of PUFA peroxy (—H_2O_2—) molecules with the help of selenium (Se). In the cytosol, the superoxide accumulation occurs due to the ETC reaction and other mitochondrial reactions. The aqueous phase superoxide ions are neutralized by superoxide dismutase enzyme. The failure of free radical—LPO reactions leads to activates cell death; proximal and distal tissue damage; and organ failure process [24]. The interaction of free radical, lipid peroxidation and toxicity mechanism is showed in **Figure 1**.

4. By-products of lipid peroxidation

The LPO of unsaturated lipids and ROS attack on unsaturated lipids are producing the variety of oxidation products. The primary oxidation products of lipid are lipid hydroperoxides (LOOH). In addition, The LPO process releases the additional by-products via metabolic conversion of lipids and their radicals. By-products of LPO are reactive aldehydes like malondialdehyde (MDA), 4-hydroxynonenal (HNE) propanal and hexanal. MDA is identified as the potent mutagenic product of lipid peroxidation; whereas, another LPO products, that is, HNE is toxic to the cellular system but not mutagenic. LPO products are categorized into two ways; first one is primary LPO product, that is, LOOH and their adduct products. Another one is the secondary LPO product, that is, MDA and their adducts [25]. Primary lipid peroxidation products (hydroperoxides) are formed at the propagation phase of the LPO process. The hydroperoxide group can be attaching to multiple lipid molecules such as free fatty acids; triacyl glycerols; phospholipids; and sterols. LOOH are more stable products and found in serum. Hence, the LPO products can be detectable for identification of cellular oxidative stress. The LOOH are targeted to various reduction reactions; which lead to either inhibition of peroxidative damage and/or induction of peroxidative damage [3]. The inhibition of peroxidative damage is due to decomposing of hydroperoxides, namely two-electron reduction [26]. Some of the enzymes are responsible for this two-electron reduction process of hydroperoxides. Those enzymes are selenium-dependent glutathione peroxidases (GPx) and selenoprotein P (SeP). The induction of peroxidative damage is due to decomposing of hydroperoxides, namely one-electron reduction in the initiation and/or propagation steps of LPO process [27]. These conditionsenhance the formation of new LOOH, that is, lipid peroxyl radical and alkoxyl radicals by redox cycling process [28].

A secondary lipid peroxidation product (MDA) is a by-product of arachidonic acid and PUFAs decomposition. This reaction occurs by enzymatic or non-enzymatic reaction process. MDA has a dose-dependent dual role function; it is chemically stable and membrane-permeable compare to ROS; whereas, MDA is less toxic than HNE and methylglyoxal (MG) products. The enzymatic production of MDA is occurred during the biosynthesis of thromboxane A_2 (TAX-A_2) from arachidonic acid metabolism by the action of TAX-A_2 synthase [29]. The non-enzymatic

production of MDA occurs with a mixture of lipid hydroperoxides during lipid peroxidation process. The non-enzymatic production of MDA is occurring under specific conditions. The metabolism of MDA involves via mitochondrial aldehyde dehydrogenase actions; which leads to form decarboxylated products, that is, acetaldehyde; and it is further oxidized by aldehyde dehydrogenase to form acetate; carbon-di-oxide (CO_2); and water (H_2O) [3].

Both primary and secondary by-products of LPO are playeda key role in the various pathophysiological process including neurodegenerative disorders. MDA and HNE products are interfering with the various biological processes such as genetic; physiological; and pathological to control the intrinsic and extrinsic factor influences [30]. In genetic aspects, LPO can be controlled by diet; environment; and habits. Various LPO studies are carried out in experimental animal models. The following agents are reported to produce the LPO in the biological system. Cumene hydroperoxide, it is used in the chemical and pharmaceutical industry as a catalytic agent [31]. Tert butyl hydroperoxide is an organic oxidizing agent and acts as a bleaching agent; and initiator of polymerization. Carbon tetrachloride (CCl_4) is a toxic carcinogenic agent and it is used as a solventfor the industrial degreasing operations. In addition, it is also used as pesticides and chemical intermediate of refrigerants. Quinolinic acid (QA) is produces the potent neurotoxic metabolite of kynurenine metabolism intermediates and involves in the pathogenesis of neurological diseases [32]. Furthermore, some of the transition metals ions also play a role for LPO process due to its pro-oxidant effect. The major transition metals for the LPO is copper; chromium; cadmium; nickel; vanadium; manganese; and iron [3, 33–35].

In aging condition; iron plays a key role in the neurological disorders. Iron accumulation in CNS causing the lipid peroxidation process and it causes the motor dysfunction and other neurological disorders [36]. Now, iron dependent cell death is linked with the lipid peroxidation process. This phenomenon also called as "*ferroptosis*". Ferroptosis is a process and produces the non-apoptotic manner of cell death regulation process [37]. This iron dependent regulation of cell death is characterized by the accumulation of LPO products. Moreover, ferroptosis process can be controlled by the lipid acting antioxidants and potent iron chelators [37, 38]. Some of the molecules are identified as ferroptosis regulators such as erastin and rat sarcoma selective lethal 3 (RSL3) proteins [39].

5. Hazards action of lipid peroxidation products

The developed LPO products must be degraded in the biological system by enzymatic and non-enzymatic manner. If the termination of oxidized LPO products is not enough; it's causing the potential tissue damage to the cell membrane. The first phase of LPO is altered by the cytosolic enzymatic and calcium pool [40]. The second phase of LPO is shown to activation of macrophage followed by oxidation of PUFA [41, 42]. In addition, LPO products also interact with multiple catalysts and heavy metals such as iron and copper metals. A ferrousform of iron is highly interactive metals with lipid peroxidative products and it also documented to produce the potent neurodegenerative process [33, 42].

The summary of LPO induced neurodegeneration is due to free radical associated activation of membrane lipid oxidation and subsequent alteration of free radical, mineral, metal and enzymatic pool activation in the cytosol of every cellular system including nervous tissue [42, 43]. In a neuron, these actions are rapid and specialized targeted proteins, that is, cytoskeleton, misfolding and prion proteins [44]. Some of the actions occur in mitochondria and nuclear levels [45]. This multiple molecular and cellular actions are responsible for the sustained activation of

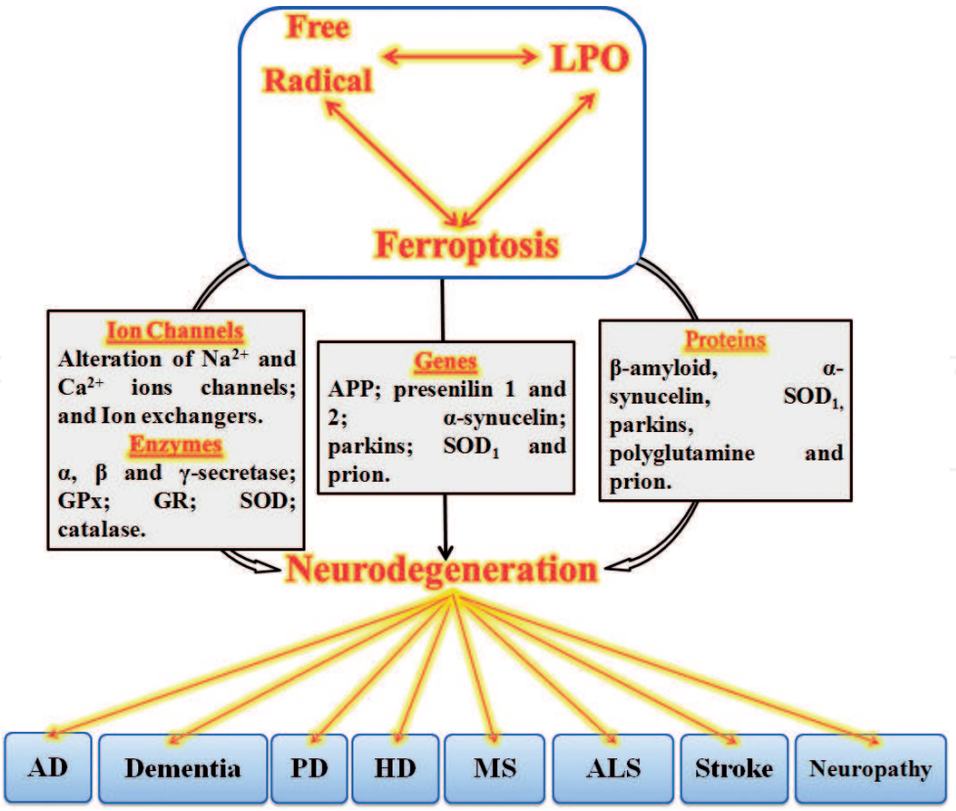

Figure 2.
Mechanism of LPO associated neurodegenerative disorders. The initial event of free radicals enhances the lipid peroxidation of products, which leads to alter the ion channels; enzymes; genes and proteins. The net effects of LPO products are cause the Alzheimer disease (AD); dementia; Parkinson's disease (PD); Huntington disease (HD); multiple sclerosis (MS); amylotropic lateral sclerosis (ALS); stroke; and neuropathy.

the neurodegenerative process leads to produce the multiple neurological disorders with neurodegeneration [46, 47]. This hazards reaction of LPO on targeted biomolecule for neurodegenerative disorders are illustrated in **Figure 2**. The following section is explaining about the LPO role in neurodegenerative disorders like Alzheimer disease (AD), Parkinson disease (PD), multiple sclerosis (MS), amylotropic lateral sclerosis (ALS), stroke and neuropathy.

6. Role of LPO in Alzheimer disease

LPO is one of the primary key factors for the progress of neurodegenerative disorders. The pathogenesis of AD is also documented that, oxidative stress enhance the progress of neurodegeneration via free radical associated LPO reactions [48]. The progress of AD rate is higher in developing countries and it causes the reduction of quality of life [49]. The various etiological factors are identified in the development of AD such as smoking, alcohol, hypertension, atherosclerosis, diabetes, hypercholesterolemia, aging and trauma. In addition, specialized neuronal proteins such as amyloid precursor protein (APP), the Aβ peptide, neurofibrillary tangles, Tau proteins, and amyloid plaques are plays a role in the alteration of neuronal function and its enhance the neurodegeneration and development of AD [50, 51]. Furthermore, these changes are due to alteration of multiple cellular signaling cascades such as over activation of α, β and γ secretase; beta-site APP-cleaving enzyme 1 and 2 ($BACE_1$ & $BACE_2$); presenilins proteins 1 and 2 (P_1 & P_2); apolipoprotein E-epsilon4 variant (ApoE-ε4); $alpha_2$-macroglobulin; and calcium dependent kinases [49, 52–55]. LPO and their metabolites contribute to the development of

neurovascular complication and neurodegeneration by activation of the above signaling pathways. Recently, ferrous ion dependent free radical generation, lipid peroxidation and activation of amyloid proteins are responsible for the development of AD [56]. The classical medicines of nootropic agents like donepezil; rivastigmine; galantamine; and memantine are enhanced the memory function [57]. Some of the agents are anti-inflammatory agent such as zileuton is regulated in the neurodegenerative process via anti-lipidperoxidative and anti-inflammatory actions [58]. However, there are limited studies reported that anti-lipid peroxidative agents are ameliorated the AD [59, 60].

7. Role of LPO in dementia

Dementia is one of the leading causes of changes in quality of life and death. Now a days, various pathophysiological factors are employed in the progression of dementia especially VaD; such conditions are hypertension, diabetic mellitus, renal failure, cardiac failure and bone fracture [61–63]. The hallmark of dementia is still complicated and some of the reports revealed that α-synuclein protein alteration enhances the neurodegeneration and dementia symptoms [64]. In addition, the genetic predisposition is identified as causing factors for dementia disorders. Recently, some of the newer molecular proteins are explored in the neurodegeneration as well as dementia such proteins are α-synuclein, ubiquitin, parkin, neurofilaments and chaperone proteins. These all changes are observed in the moderate and chronic condition of dementia disorders. Whereas, the initial effects of the neurodegeneration process is to express the development of free radical and LPO associated oxidative stress environments in the nervous system [18]. However, the specific molecules for the LPO regulators are not studied in dementia disorders. Whereas, numerous studies revealed that, the memory enhancing drugs like donepezil; rivastigmine; galantamine; and mementine are reduced the lipid peroxidative products reaction. Hence, the direct and specific modulatory agents are required for the management of dementia disorders [65]. Further, dementia disorders are arising with multiple pathophysiological factors; so the multi-targeted drug approaches will be more effective to prevent the dementia disorders. Here, the LPO targeted drugs is one of the primary facts for the treatment of dementia disorders.

8. Role of LPO in Parkinson disease

Parkinson disease (PD) is one of the extrapyramidal disorders and it occurs due to dopaminergic neurodegeneration and alteration of dopamine levels in the brain. Symptomatically, it affects the motor neuron and produces the abnormalities of body movements. The LPO process induces the primary form of sporadic type of Parkinson disease (PD) [66]. Mainly, dopaminergic neuron damage occurs in the substantia nigra, locus ceruleus, dorsal motor nucleus and substantia innominata [67]. The sign of movement problems is festinating gait; rigidity of limbs; poverty of voluntary movement; and rolling type of tremor. The progressiveness of PD is very slow [68]. The various types of cells are employed in the dopaminergic neurodegeneration such as neutrophils; macrophages; and astrocytosis [69]. This all process is altered by free radicals and lipid peroxidative reactions. LPO reactions affect multiple biomolecules such as such as membrane lipids, proteins (especially α-synculein); mitochondrial pore; endoplasmic reticulum; liposomes; peroxisomes; lysomes including DNA and RNA [51]. Therefore, the reduction and controlling LPO process is able to treat the PD. However, the limited agents are tested in the

management of dopaminergic neurodegeneration. Hence, the more extensive studies are required for the treatment of PD with direct and specific anti-lipid peroxidative drugs or combination with subsequent cell signal arresting molecules [70, 71].

9. Role of LPO in Huntington disease

Huntington disease (HD) is one of the autosomal dominant diseases. And, it is also one of the neurodegenerative disorders. It occurs between the age of 20 and 50 years. The symptoms of HD are a chorei form of body movements; dystonia; the paucity of movement and progressive loss of neuron [45]. Genetically, it affects the 4th chromosomal gene; huntingtin (HTT) protein mutation and misfolding. The main area of the brain is affection in caudate; putamen nucleous; globus pallidus; and nucleus accumbens leads to cause the atrophy of brain via the neurodegenerative process [32, 72]. The microscopical observation revealed that small spiny neurons of the caudate and putamen cause the astrocytosis. The chronic event of cellular neurodegenerative process enhances the neuronal oxidative stress with an accumulation of free radicals and LPO process [73]. During the early stage of LPO process; neuronal cells losses the cell contents; shrinkage of caudate nucleolus; shrinkage and dilatation of the anterior horns of lateral ventricles [45, 72]. Moreover, LPO process enhances the alteration of various neurotransmitters such as a gamma aminobutyric acid (GABA); acetylcholine; and substance P [74, 75]. The various medicines are reported to treat the HD via inhibition of LPO process [76]. Therefore, LPO targeted medicines are useful for the management of HD and neurodegenerative disorders.

10. Role of LPO in multiple sclerosis

Multiple sclerosis (MS) is a known demyelinating disease and its causes the dysfunction of the central nervous system. Myelin produces the insulation coating on the nervous system like electrical wires. The pathogenesis of MS is shown by attacks of neuronal proteins of CNS such as myelin proteins. In addition, the LPO products are play key role in the pathogenesis of MS [77]. This myelin protein is essential for neuronal function because of its support of the neuronal signal conduction without loss of strength. Whereas, the loss of myelin proteins by immunological abnormalities are cause the neuronal dysfunction and symptoms of MS. Further, these neuronal damages are permanent and difficult to the MS [78]. The symptoms of MS are numbness or weakness in limbs, one side of your body, legs and trunk; partial or complete loss of vision and double vision; tingling and pain; tremor, lack of coordination, unsteady gait, slurred speech, fatigue, dizziness; and bowel and bladder function. These all symptoms are due to damage of myelin proteins of CNS [79]. The various factors are employed in the pathogenesis of MS such as genetic abnormalities; environmental factors (smoking and alcohol); and autoimmune disease (thyroid disease, type 1 diabetes and inflammatory bowel disease) [80]. The MS is a progressive demyelinating process, which is due to the over the action of the immunological system. The immunological proteins are inducing the multiple physiological processes. Whereas the over activity of immunological proteins causes the neurological damage via activation of the demyelinating process [81]. This chronic progressive is due to the free radical and LPO process. The limited drugs are used for the treatment of MS and it also documented that, reduce the LPO products accumulation. However, the LPO targeted drugs are not tested in MS disease. So, extensive studies are required LPO targeted medicine for the treatment of MS.

11. Role of LPO in amylotropic lateral sclerosis

Amyotrophic lateral sclerosis (ALS) is another neurodegenerative disorder of a nervous system and it affects the CNS nerve cells. In addition, it affects the neuronal transmission between the brain and the spinal cord. This leads to affects the neuromuscular function and produces the trouble for walking, running and writing; and speech problems [82]. In addition, it also produces the respiratory failure; it is a very serious complication of ALS. The primary target of neurological damage is upper motor neurons of cranial motor nuclei, and Betz cells of neocortex lead to produce the muscle atrophy and astrocytosis [83]. Sometimes ALS is also produced in the lateral column degeneration with gliosis; so it is called "sclerosis". The primary etiology of ALS is due to the mutations of superoxide dismutase-1 (SOD1) gene [78]. The SOD gene associated proteins are responsible for the reduction of cellular free radicals leads to reduce the LPO products associated with protein and DNA damage [74, 84]. Therefore, LPO targeted drug is essential for the treatment of ALS. However, there is no report is documented for the treatment of ALS.

12. Role of LPO in stroke

Stroke is one more neurodegeneration disorders and it occurs due to the cerebrovascular accidents. The primary symptoms of stroke are a cluster headache, motor impairment, paralysis and death [85–87]. The various risk factors are employed in the pathogenesis of strokes such as smoking, alcohol, obesity, trauma, hypertension, diabetes and renal failure [88, 89]. In addition, various physiological processes are altered with multiple ethiological factors such as hypoxia, ischemia, aneurysm and immune activation leads to platelet activation, thrombosis, immune cell activation decreasing of ATP content, mitochondrial damage, ionic imbalance and glial cell activation [90–92]. Furthermore, the chronic neurological damage is due to the accumulation of lipid peroxidative products leads to damage to the neurological system leads to produce the stroke symptom [93, 94]. The free radical and LPO are well documented to produce neurodegeneration in stroke condition [95]. However, the tested compounds are show in the alteration of LPO products in the neurological system. But, the direct and specific action on LPO products is not documented in stroke disorders. So, the extensive studies are required to manage the stroke disorders with direct and newer molecule for the reduction of LPO products [96].

13. Role of LPO in neuropathy

The pathogenesis of neuropathy is occurred due to the neurodegenerative disorders. In diabetic condition, it produces the multiple types like autonomic neuropathy, somatic neuropathy, peripheral and central neuropathy. The etiology of neuropathy is due to multiple factors such as ischemia, trauma, hypoxia, free radical and lipid peroxidation [9, 97]. These factors alter the cellular and molecular events [98, 99]. The anatomy of microvascular system is affecting by the above factors and it raising the oxidative stress environment along with DNA damage, ATP depletion and activation of ferroptosis [100]. The symptoms of neuropathy are the development of autotomy (self-amputation of figures); allodynia (triggering of a pain response from stimuli, but it does not provoke pain in normal condition); hyperalgesia (extreme reaction of painful stimuli); and numbness (unusual prickling sensation). The chronic condition of neuronal firing enhances the neurodegeneration and reduces the quality of life [101]. In diabetic condition, the

specialized etiology involved in the pathogenesis of neuropathy; such factors are raising blood glucose, sorbitol, aldose, ketone bodies; and advanced glycation end products (AGE) [102]. This all molecules are interlinked with oxidative stress. The accumulation of free radicals and the LPO process involves in the all pathological situation of neuropathy and neurodegenerative process; which leads to producing the subsequent activation of ionic imbalance; vascular damage; and neuronal damage [103, 104]. The LPO products play a crucial role in the pathogenesis of neuropathy [105, 106]. However, the directly acting agents on LPO products and specific molecules based actions still need to investigate for the management of neuropathy [107].

14. Inhibiting of LPO products

The various approaches are attempted to prevent the LPO products formation. There are two approaches are employed in the prevention of LPO products such as (1) prevention of LPO products formation by both enzymatic and non-enzymatic manner; (2) elimination of LPO products [108, 109]. Prevention of LPO products formation is a primary successful method with anti-oxidants such as vitamin C and vitamin E are inhibits the LPO [110]. The alternative method of LPO inhibition is deuteration of PUFA at double bond of methylene bridges (bis-allylic sites) leads to reduce the chain reaction process [111]. The major deuteriated PUFAs is 11,11-D2-ethyl linoleate is identified as suppressing agent for LPO process at low level concentration [112]. The primary diagnostic methods for end-products of LPO, that is, malondialdehyde (MDA) is thiobarbituric acid reactive substances (TBARS) assay. Recently, some immunochemical method is employed for the detection of HNE-histidine adducts in biological tissue and fluid samples [113]. Based on this basic fundamental of LPO formation and diagnostic procedure; some of the molecules are identified for the prevention of LPO process and products formation [114]. Some of the molecules are documented that, it prevents the neurodegenerative process via alteration of the various cellular signaling process. Some of LPO peroxides are formed by lipoxygenase enzymatic system. Thus, 5-lipoxygenase (5-LOX) inhibitor, that is, zileuton employed as a reduction of LPO products in the biological system via ligation of the active site of iron through its N-hydroxy urea moiety [58]. In addition, the 12- and 15-lipoxygenases (12-LOX and 15-LOX) process contributes to the significant role in the pathogenesis of neurodegenerative disorders via accumulation of LPO products [115]. The discovery of 12-LOX and 15-LOX inhibitors is still developing stage. The isotope of deuterated of PUFA products are documented to prevents the LPO products via enzymatic and non-enzymatic manner [18, 115]. Elimination of peroxides: the limited quantity of LPO products formation and reduction is not harmful to the cellular system. Whereas, the abundant accumulation of LPO products makes the serious complication to the biological system via alternating cell signal and functions [116]. Generally, the biological system eliminates the LPO products via the enzymatic mechanism [117, 118]. The glutathione peroxidase (GPx) enzyme is one of the classical enzymes for reduction of LPO products. Total eight isoforms of GPx enzymes are distributed in humans with different substrate specificities and tissue specificity. Among all GPx enzymes, the GPx4 is identified as a primary enzyme for the reduction of lipid peroxides. In addition, it also interferes with ferrous ion leads to reduce the ferroptotic cell death and accumulation of toxic lipid peroxides [40]. Another cofactor, that is, selenocysteine also helps to enhance the GPx4 enzyme activity for reduction of lipid peroxides using due to its strong nucleophilic attack on the terminal oxygen of lipid peroxide [119]. This reaction helps to the reduction

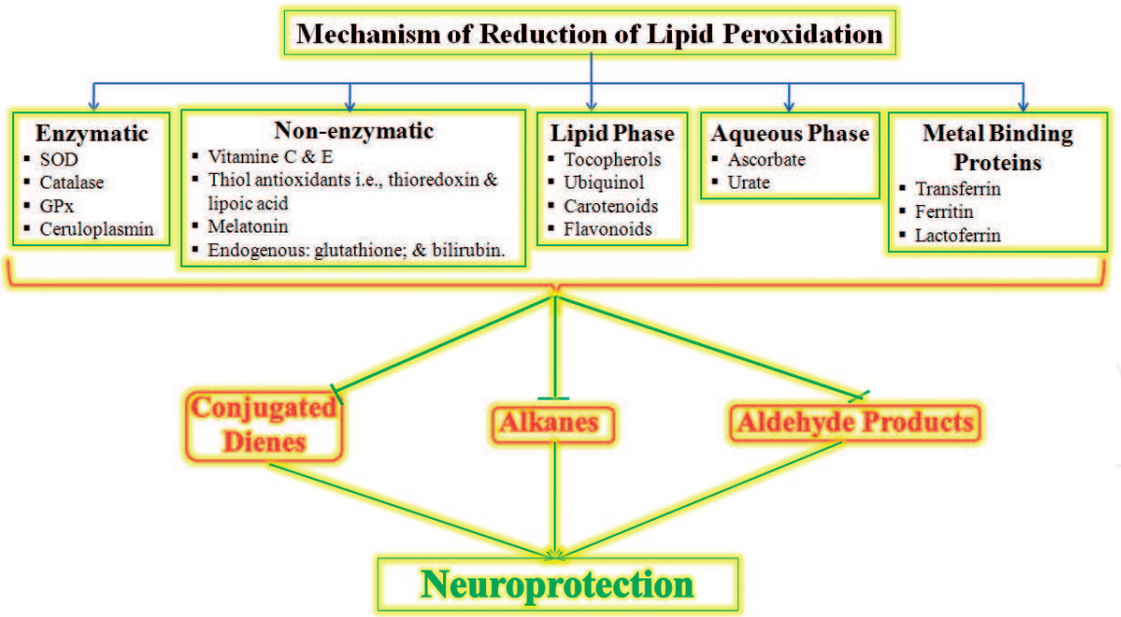

Figure 3.
Mechanism of reduction of lipid radicals. The primary event of lipid radicals is ROS formation. Thus, various antioxidant molecules are claimed as anti-lipid peroxidative agents. These agents are also known as free radical scavengers. This anti-oxidative molecules are categorized into the five ways, that is, enzymatic; non-enzymatic; lipid phase; solid phase actions; and activation of metal binding protein actions. The free radical scavenging molecules are reduce and termination the lipid radical in the biological system leads to neuroprotection from toxic radicals.

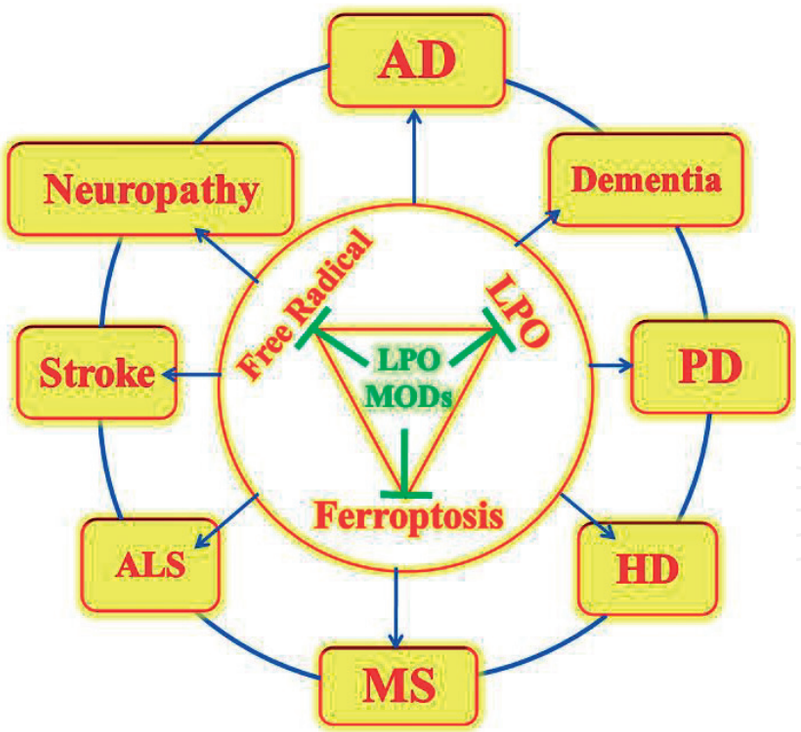

Figure 4.
Mechanism of LPO modulators for the prevention of neurodegenerative disorders. There are three major interrelated functions are inducing the neurodegeneration and neurological disorders such as (1) free radical generation; (2) LPO product accumulation; and (3) ferroptosis. The LPO modulators are attenuated the neurodegenerative disorders like anti-oxidant; anti-lipid peroxidation; and iron chelating actions.

of hydroxyeicosatetraenoic acid (HETE) or hydroxyoctadecadienoic acid (HODE) accumulation in the biological system. Furthermore, selenenic acid intermediates are reduced by the two molecules of oxidized glutathione and regenerate the active GPx enzyme [120]. List of LPO regulating molecules is listed in **Figures 3** and **4**.

15. Summary of LPO in neurodegenerative disorders

LPO products are contributes to the various types of neurodegenerative disorders such as AD, dementia, PD, HD, MS, ALS, stroke and neuropathy [108]. However, the availability of LPO products regulating molecules is limited. Their molecular action in *in-vivo* biological actions is not explored yet. Hence, the extensive researches are required to prove the potential ameliorative effect of LPO acting molecules to prevent the neurodegenerative disorders.

16. Future directions

Based on this complete literature and research reports, LPO regulating molecules has ample scope to prevent the neurodegenerative disorders. Because LPO products are documented to play a critical role in the various stage of the neurodegenerative disease. Even, it also interferes with multiple cell organelles such as mitochondria, endoplasmic reticulum, lysosome, peroxisome, nucleus and various cytoskeletal proteins. The numerous reports also documented that, the molecules are altering the LPO process and reducing the LPO products accumulations. Whereas, all the classical neuroprotective drugs are claimed as ion channel regulator; enzyme modulators; receptor antagonist actions so on. The direct and specific LPO pathway regulating molecules are not identified to attenuate the neurodegenerative disorders in vivo pharmacological research. Even, the newer concept of LPO associated ferroptosis actions enhances the neurodegeneration, but ferroptosis regulating molecules in the management of neurodegenerative disorders need to be study extensively. So, the discovery of LPO pathway modulating agents can treat the neurodegenerative disorders. Hence, we believe that, this book chapter will be helpful to the various researchers; who working on newer molecule discovery process for the prevention of LPO associated neurodegenerative disorders.

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References

[1] Nita M, Grzybowski A. The role of the reactive oxygen species and oxidative stress in the pathomechanism of the age-related ocular diseases and other pathologies of the anterior and posterior eye segments in adults. Oxidative Medicine and Cellular Longevity. 2016;**2016**:3164734

[2] Barone E et al. HNE-modified proteins in Down syndrome: Involvement in development of Alzheimer disease neuropathology. Free Radical Biology and Medicine. 2017;**111**:262-269

[3] Ayala A, Muñoz MF, Argüelles S. Lipid peroxidation: Production, metabolism, and signaling mechanisms of malondialdehyde and 4-hydroxy-2-nonenal. Oxidative Medicine and Cellular Longevity. 2014;**2014**:360438

[4] Sergeeva I. Structural-metabolic characteristics of cells and their functional opportunities. 2018:**1**(1):1-7

[5] Yang WS et al. Peroxidation of polyunsaturated fatty acids by lipoxygenases drives ferroptosis. Proceedings of the National Academy of Sciences. 2016;**113**(34):E4966-E4975

[6] Das K, Roychoudhury A. Reactive oxygen species (ROS) and response of antioxidants as ROS-scavengers during environmental stress in plants. Frontiers in Environmental Science. 2014;**2**:53

[7] Birben E et al. Oxidative stress and antioxidant defense. World Allergy Organization Journal. 2012;**5**(1):9

[8] Sheikh S, Haque E, Mir SS. Neurodegenerative diseases: Multi-factorial conformational diseases and their therapeutic interventions. Journal of Neurodegenerative Diseases. 2012;**2013**:563481

[9] Perez-Matos M, Morales-Alvarez M, Mendivil C. Lipids: A suitable therapeutic target in diabetic neuropathy? Journal of Diabetes Research. 2017;**2017**:6943851

[10] Aprioku JS. Pharmacology of free radicals and the impact of reactive oxygen species on the testis. Journal of Reproduction & Infertility. 2013;**14**(4):158

[11] Nowak JZ. Oxidative stress, polyunsaturated fatty acids derived oxidation products and bisretinoids as potential inducers of CNS diseases: Focus on age-related macular degeneration. Pharmacological Reports. 2013;**65**(2):288-304

[12] Gutowski M, Kowalczyk S. A study of free radical chemistry: Their role and pathophysiological significance. Acta Biochimica Polonica. 2013;**60**(1):1-16

[13] Ortiz GG et al. Cellular and biochemical actions of melatonin which protect against free radicals: Role in neurodegenerative disorders. Current Neuropharmacology. 2008;**6**(3):203-214

[14] Phaniendra A, Jestadi DB, Periyasamy L. Free radicals: Properties, sources, targets, and their implication in various diseases. Indian Journal of Clinical Biochemistry. 2015;**30**(1):11-26

[15] Nicolson GL, Ash ME. Membrane lipid replacement for chronic illnesses, aging and cancer using oral glycerolphospholipid formulations with fructooligosaccharides to restore phospholipid function in cellular membranes, organelles, cells and tissues. Biochimica et Biophysica Acta (BBA)-Biomembranes. 2017;**1859**(9):1704-1724

[16] Rafieian-Kopaei M et al. Atherosclerosis: Process, indicators, risk factors and new hopes. International Journal of Preventive Medicine. 2014;**5**(8):927

[17] Gahalain N et al. Lipid peroxidation: An overview. International Journal of Pharmaceutical Sciences and Research. 2011;**2**(11):2757

[18] Raefsky SM et al. Deuterated polyunsaturated fatty acids reduce brain lipid peroxidation and hippocampal amyloid β-peptide levels, without discernable behavioral effects in an APP/PS1 mutant transgenic mouse model of Alzheimer's disease. Neurobiology of Aging. 2018;**66**:165-176

[19] Bhat AH et al. Oxidative stress, mitochondrial dysfunction and neurodegenerative diseases; a mechanistic insight. Biomedicine & Pharmacotherapy. 2015;**74**:101-110

[20] Di Domenico F, Tramutola A, Butterfield DA. Role of 4-hydroxy-2-nonenal (HNE) in the pathogenesis of alzheimer disease and other selected age-related neurodegenerative disorders. Free Radical Biology and Medicine. 2017;**111**:253-261

[21] Kurutas EB. The importance of antioxidants which play the role in cellular response against oxidative/nitrosative stress: Current state. Nutrition Journal. 2015;**15**(1):71

[22] Guengerich FP, Yoshimoto FK. Formation and cleavage of C—C bonds by enzymatic oxidation–reduction reactions. Chemical Reviews. 2018;**118**(14):6573-6655

[23] Maeda H et al. Tocopherols modulate extraplastidic polyunsaturated fatty acid metabolism in Arabidopsis at low temperature. The Plant Cell. 2008;**20**(2):452-470

[24] Yin H, Xu L, Porter NA. Free radical lipid peroxidation: Mechanisms and analysis. Chemical Reviews. 2011;**111**(10):5944-5972

[25] Bradley-Whitman MA, Lovell MA. Biomarkers of lipid peroxidation in Alzheimer disease (AD): An update. Archives of Toxicology. 2015;**89**(7):1035-1044

[26] Remello SN et al. Two-electron oxidation of water to form hydrogen peroxide catalysed by silicon-porphyrins. Sustainable Energy & Fuels. 2018;**2**(9):1966-1973

[27] Kagan VE. Lipid peroxidation. In: Biomembranes. New York: CRC Press; 2018

[28] Zoidis E et al. Selenium-dependent antioxidant enzymes: Actions and properties of selenoproteins. Antioxidants. 2018;**7**(5):66

[29] Matsunobu T et al. Thromboxane A synthase-independent production of 12-hydroxyheptadecatrienoic acid, a BLT2 ligand. Journal of Lipid Research. 2013;**54**(11):2979-2987

[30] Yang C, Shahidi F, Tsao R. Biomarkers of oxidative stress and cellular-based assays of indirect antioxidant measurement. Measurement of Antioxidant Activity and Capacity: Recent Trends and Applications. 2018. p. 165. ISBN: 978-1-119-13535-7

[31] Saieva C et al. Dietary and lifestyle determinants of malondialdehyde DNA adducts in a representative sample of the Florence City population. Mutagenesis. 2016;**31**(4):475-480

[32] Sathyasaikumar KV et al. Assessing and Modulating Kynurenine Pathway Dynamics in Huntington's Disease: Focus on Kynurenine 3-Monooxygenase, in Huntington's Disease. New York: Springer; 2018. pp. 397-413

[33] Farina M et al. Metals, oxidative stress and neurodegeneration: A focus on iron, manganese and mercury. Neurochemistry International. 2013;**62**(5):575-594

[34] Ijomone OM et al. Sub-acute nickel exposure impairs behavior, alters neuronal microarchitecture, and induces oxidative stress in rats' brain. Drug and Chemical Toxicology. 2018;**26**:1-8

[35] Kumar A et al. Biochemical and Molecular Targets of Heavy Metals and their Actions, in Biomedical Applications of Metals. Switzerland: Springer; 2018. pp. 297-319

[36] Lane DJ, Ayton S, Bush AI. Iron and alzheimer's disease: An update on emerging mechanisms. Journal of Alzheimer's Disease. 2018;**64**(S1):1-16

[37] Conrad M et al. Regulation of lipid peroxidation and ferroptosis in diverse species. Genes & Development. 2018;**32**(9-10):602-619

[38] Feng H, Stockwell BR. Unsolved mysteries: How does lipid peroxidation cause ferroptosis? PLoS Biology. 2018;**16**(5):e2006203

[39] Morris G et al. Why should neuroscientists worry about iron? The emerging role of ferroptosis in the pathophysiology of neuroprogressive diseases. Behavioural Brain Research. 2017;**341**:154-175

[40] Maiorino M, Conrad M, Ursini F. GPx4, lipid peroxidation, and cell death: Discoveries, rediscoveries, and open issues. Antioxidants & Redox Signaling. 2018;**29**(1):61-74

[41] Song Y et al. Polyunsaturated fatty acid relatively decreases cholesterol content in THP-1 macrophage-derived foam cell: Partly correlates with expression profile of CIDE and PAT members. Lipids in Health and Disease. 2013;**12**(1):111

[42] Sergent O, Morel I, Cillard J. Involvement of metal ions in lipid peroxidation: Biological implications. Metal Ions in Biological Systems. 1999;**36**:251-287

[43] Garza-Lombó C et al. Neurotoxicity linked to dysfunctional metal ion homeostasis and xenobiotic metal exposure: Redox signaling and oxidative stress. Antioxidants & Redox Signaling. 2018;**28**(18):1669-1703

[44] Yaribeygi H et al. The underlying role of oxidative stress in neurodegeneration: A mechanistic review. CNS & Neurological Disorders-Drug Targets. 2018;**17**(3):207-215

[45] Agrawal S et al. Brain mitochondrial iron accumulates in Huntington's disease, mediates mitochondrial dysfunction, and can be removed pharmacologically. Free Radical Biology and Medicine. 2018;**120**:317-329

[46] Cortes CJ, La Spada AR. TFEB dysregulation as a driver of autophagy dysfunction in neurodegenerative disease: Molecular mechanisms, cellular processes, and emerging therapeutic opportunities. Neurobiology of Disease. 2018;**18**:30150-30155

[47] Flanagan E et al. Impact of flavonoids on cellular and molecular mechanisms underlying age-related cognitive decline and neurodegeneration. Current Nutrition Reports. 2018;**7**(2):49-57

[48] Ansari MA, Scheff SW. Oxidative stress in the progression of Alzheimer disease in the frontal cortex. Journal of Neuropathology & Experimental Neurology. 2010;**69**(2):155-167

[49] Mecocci P et al. A long journey into aging, brain aging, and Alzheimer's disease following the oxidative stress tracks. Journal of Alzheimer's Disease. 2018;**62**(3):1319-1335

[50] Janocko NJ et al. Neuropathologically defined subtypes of Alzheimer's disease differ significantly from neurofibrillary tangle-predominant dementia. Acta Neuropathologica. 2012;**124**(5):681-692

[51] Choi ML, Gandhi S. Crucial role of protein oligomerization in the pathogenesis of Alzheimer's and Parkinson's diseases. The FEBS Journal. 2018. DOI: 10.1111/febs.14587. (Article in press)

[52] Gaj P et al. Identification of a late onset Alzheimer's disease candidate risk variant at 9q21.33 in Polish patients. Journal of Alzheimer's Disease. 2012;**32**(1):157-168

[53] Shinohara M et al. Regional distribution of synaptic markers and APP correlate with distinct clinicopathological features in sporadic and familial Alzheimer's disease. Brain. 2014;**137**(Pt 5):1533-1549

[54] Yuan Q et al. Association of polymorphisms in the LRP1 and A2M genes with Alzheimer's disease in the northern Chinese Han population. Journal of Clinical Neuroscience. 2013;**20**(2):253-256

[55] Vinothkumar G et al. Therapeutic impact of rHuEPO on abnormal platelet APP, BACE 1, presenilin 1, ADAM 10 and Aβ expressions in chronic kidney disease patients with cognitive dysfunction like Alzheimer's disease: A pilot study. Biomedicine & Pharmacotherapy. 2018;**104**:211-222

[56] Atwood CS et al. Role of free radicals and metal ions in the pathogenesis of Alzheimer's disease. Metal Ions in Biological Systems. 1999;**36**:309-364

[57] Kalász H et al. Pharmacognostical sources of popular medicine to treat Alzheimer's disease. The Open Medicinal Chemistry Journal. 2018;**12**:23

[58] Panigrahi S et al. 5-lipoxygenase: Emerging therapeutic targets in central nervous system disorders. International Journal of Advanced Research in Biological Sciences. 2018;**5**(3):20-29

[59] Verma SK et al. Enhancement in the neuroprotective power of riluzole against cerebral ischemia using a brain targeted drug delivery vehicle. ACS Applied Materials & Interfaces. 2016;**8**(30):19716-19723

[60] Butterfield DA, Lange MLB, Sultana R. Involvements of the lipid peroxidation product, HNE, in the pathogenesis and progression of Alzheimer's disease. Biochimica et Biophysica Acta (BBA)-Molecular and Cell Biology of Lipids. 2010;**1801**(8):924-929

[61] Than S, Srikanth V. Detecting brain injury related to hypertension at midlife—A key to interventions for preventing dementia in older age. Cardiovascular Research. 2018;**114**:1430-1431

[62] Kondo S, Kondo Y. Association of the types of dementia and the incidence of hypertension, diabetes mellitus, or bone fracture. Gan to kagaku ryoho. Cancer & Chemotherapy. 2018;**45**(Suppl 1):25-26

[63] Jordan BC et al. Dementia as a predictor of mortality in adult trauma patients. The American Journal of Surgery. 2018;**215**(1):48-52

[64] Zhang S et al. Intercellular transfer of pathogenic α-synuclein by extracellular vesicles is induced by the lipid peroxidation product 4-hydroxynonenal. Neurobiology of Aging. 2018;**61**:52-65

[65] Yadav A et al. Resveratrol loaded solid lipid nanoparticles attenuate mitochondrial oxidative stress in vascular dementia by activating Nrf2/HO-1 pathway. Neurochemistry International. 2018;**112**:239-254

[66] Bastías-Candia S, Zolezzi JM, Inestrosa NC. Revisiting the paraquat-induced sporadic Parkinson's disease-like model. Molecular Neurobiology. 2018. DOI: 10.1007/s12035-018-1148-z. (Article in press)

[67] Jaswal G et al. Reduced substantia innominata volume mediates contributions of microvascular and macrovascular disease to cognitive deficits in Alzheimer's disease. Neurobiology of Aging. 2018;**66**:23-31

[68] Ehara A et al. Role of neuronal nitric oxide synthase in slowly progressive dopaminergic neurodegeneration in the Zitter rat. Nitric Oxide. 2018;**78**:41-50

[69] Joe E-H et al. Astrocytes, microglia, and Parkinson's disease. Experimental Neurobiology. 2018;**27**(2):77-87

[70] Angelova PR et al. Lipid peroxidation is essential for α-synuclein-induced cell death. Journal of Neurochemistry. 2015;**133**(4):582-589

[71] Rachitha P et al. Chemical composition, antioxidant potential, macromolecule damage and neuroprotective activity of Convolvulus pluricaulis. Journal of Traditional and Complementary Medicine. 2018. DOI: ORG/10.1016/J.JTCME.2017.11.002. (Article in press)

[72] Lecumberri A et al. Neuronal density and proportion of interneurons in the associative, sensorimotor and limbic human striatum. Brain Structure and Function. 2018;**223**(4):1615-1625

[73] Esparza JL, Gómez M, Domingo JL. Role of melatonin in aluminum-related neurodegenerative disorders: A review. Biological Trace Element Research. 2018. DOI: 10.1007/s12011-018-1372-4. (Article in press)

[74] Vallée A et al. Aerobic glycolysis in amyotrophic lateral sclerosis and Huntington's disease. Reviews in the Neurosciences. 2018;**29**(5):547-555

[75] Jaglan D, Singh Bindra C. Evaluating neuroprotective effects of ascorbic acid against 3-nitropropionic acid induced huntington's disease in rats. Possible Involvement of Gabaareceptors. 2018;**6**(2):33-68

[76] Lee C-T et al. Current advances in the biological activity of polysaccharides in Dendrobium with intriguing therapeutic potential. Current Medicinal Chemistry. 2018;**25**(14):1663-1681

[77] Tully M et al. Systemic acrolein elevations in mice with experimental autoimmune encephalomyelitis and patients with multiple sclerosis. Frontiers in Neurology. 2018;**9**:420-429

[78] Sheykhansari S et al. Redox metals homeostasis in multiple sclerosis and amyotrophic lateral sclerosis: A review. Cell Death & Disease. 2018;**9**(3):348

[79] Elshaer ARM et al. Approach in diagnosis and management and common mistakes in diagnosis of multiple sclerosis. Egyptian Journal of Hospital Medicine. 2018;**70**(11):2008-2015

[80] Alfredsson L, Olsson T. Lifestyle and environmental factors in multiple sclerosis. Cold Spring Harbor Perspectives in Medicine. 2018. DOI: 10.1101/cshperspect.a028944. (Article in press)

[81] Campbell G, Mahad D. Neurodegeneration in progressive multiple sclerosis. Cold Spring Harbor Perspectives in Medicine. 2018. DOI: 10.1101/cshperspect.a028985. (Article in press)

[82] Pennetta G, Welte MA. Emerging links between lipid droplets and motor neuron diseases. Developmental Cell. 2018;**45**(4):427-432

[83] Hasegawa I et al. An autopsy case of globular glial tauopathy presenting with clinical features of motor neuron disease with dementia and iron deposition in the motor cortex. Neuropathology. 2018;**38**:372-379

[84] Komatsu K et al. Overexpressed wild-type superoxide dismutase 1

exhibits amyotrophic lateral sclerosis-related misfolded conformation in induced pluripotent stem cell-derived spinal motor neurons. Neuroreport. 2018;**29**(1):25-29

[85] Debette S et al. Association of MRI markers of vascular brain injury with incident stroke, mild cognitive impairment, dementia, and mortality: The Framingham Offspring Study. Stroke. 2010;**41**(4):600-606

[86] Krueger M et al. Blood-brain barrier breakdown after embolic stroke in rats occurs without ultrastructural evidence for disrupting tight junctions. PLoS One. 2013;**8**(2):e56419

[87] Gaignard P et al. Sex differences in brain mitochondrial metabolism: Influence of endogenous steroids and stroke. Journal of Neuroendocrinology. 2018;**30**(2):e12497

[88] Stecker M et al. Risk factors for DVT/PE in patients with stroke and intracranial hemorrhage. Open Neurology Journal. 2014;**8**:1-6

[89] Price AJ et al. Differences in risk factors for 3 types of stroke: UK prospective study and meta-analyses. Neurology. 2018;**90**(4):e298-e306

[90] Kong LL et al. Neutralization of chemokine-like factor 1, a novel C-C chemokine, protects against focal cerebral ischemia by inhibiting neutrophil infiltration via MAPK pathways in rats. Journal of Neuroinflammation. 2014;**11**:112

[91] Foreman PM et al. Endothelin polymorphisms as a risk factor for cerebral aneurysm rebleeding following aneurysmal subarachnoid hemorrhage. Clinical Neurology and Neurosurgery. 2017;**157**:65-69

[92] Vidale S et al. Post-ischemic inflammation in acute stroke. Journal of Clinical Neurology. 2017;**13**(1):1-9

[93] Goldstein LB et al. Primary prevention of ischemic stroke: A guideline from the American heart association/American stroke association stroke council: Cosponsored by the atherosclerotic peripheral vascular disease interdisciplinary working group; cardiovascular nursing council; clinical cardiology council; nutrition, physical activity, and metabolism council; and the quality of care and outcomes research interdisciplinary working group: The American academy of neurology affirms the value of this guideline. Stroke. 2006;**37**(6):1583-1633

[94] Tsikas D. Assessment of lipid peroxidation by measuring malondialdehyde (MDA) and relatives in biological samples: Analytical and biological challenges. Analytical Biochemistry. 2017;**524**:13-30

[95] Sun M-S et al. Free radical damage in ischemia-reperfusion injury: An obstacle in acute ischemic stroke after revascularization therapy. Oxidative Medicine and Cellular Longevity. 2018;**2018**:3804979

[96] Sayre LM, Perry G, Smith MA. Oxidative stress and neurotoxicity. Chemical Research in Toxicology. 2007;**21**(1):172-188

[97] Mrakic-Sposta S et al. R (+)-Thioctic acid effects on oxidative stress and peripheral neuropathy in type II diabetic patients: Preliminary results by electron paramagnetic resonance and electroneurography. Oxidative Medicine and Cellular Longevity. 2018;**2018**:1767265

[98] Hlusicka J et al. Role of activation of lipid peroxidation in the mechanisms of acute methanol poisoning. Clinical Toxicology. 2018. p. 1-11. DOI: 10.1080/15563650.2018.1455980

[99] Inoue K, Tsuda M. Microglia in neuropathic pain: Cellular and molecular mechanisms and

therapeutic potential. Nature Reviews Neuroscience. 2018;**19**(3):138-152

[100] Morris G et al. Cell death pathways: A novel therapeutic approach for neuroscientists. Molecular Neurobiology. 2018;**55**(7):5767-5786

[101] Rice AS et al. Sensory profiling in animal models of neuropathic pain: A call for back-translation. Pain. 2018;**159**(5):819-824

[102] Dewanjee S et al. Molecular mechanism of diabetic neuropathy and its pharmacotherapeutic targets. European Journal of Pharmacology. 2018;**833**:472-523

[103] Sengupta A et al. Balance between antioxidant enzyme and lipid peroxidation in diabetes neuropathy. Balance. 2018;**3**(2):1125-1128

[104] Apostolopoulou K et al. Ischemia–reperfusion injury of sciatic nerve in rats: Protective role of combination of vitamin C with E and tissue plasminogen activator. Neurochemical Research. 2018;**43**(3):650-658

[105] Muthuraman A, Ramesh M. Ischemic-reperfusion of unilateral external iliac artery in rat: A new model for vasculitic femoral neuropathy. Neuroscience Letters. 2016;**628**:10-16

[106] Muthuraman A, Singla SK, Peters A. Exploring the potential of flunarizine for cisplatin-induced painful uremic neuropathy in rats. International Neurourology Journal. 2011;**15**(3):127-134

[107] Frank B, Gupta S. A review of antioxidants and Alzheimer's disease. Annals of Clinical Psychiatry. 2005;**17**(4):269-286

[108] Sottero B et al. Lipid oxidation derived aldehydes and oxysterols between health and disease. European Journal of Lipid Science and Technology. 2018. p. 1700047. DOI: ORG/10.1002/EJLT.201700047

[109] Mirończuk-Chodakowska I, Witkowska AM, Zujko ME. Endogenous non-enzymatic antioxidants in the human body. Advances in Medical Sciences. 2018;**63**(1):68-78

[110] Mehta V et al. ACE Alzheimer's: The role of vitamin A, C and E (ACE) in oxidative stress induced Alzheimer's disease. Journal of Medical Research and Innovation. 2018;**2**(1):e000086-e000086

[111] Xiao M et al. Pathophysiology of mitochondrial lipid oxidation: Role of 4-hydroxynonenal (4-HNE) and other bioactive lipids in mitochondria. Free Radical Biology and Medicine. 2017;**111**:316-327

[112] Elharram A et al. Deuterium-reinforced polyunsaturated fatty acids improve cognition in a mouse model of sporadic Alzheimer's disease. The FEBS Journal. 2017;**284**(23):4083-4095

[113] Zarkovic K, Jakovcevic A, Zarkovic N. Contribution of the HNE-immunohistochemistry to modern pathological concepts of major human diseases. Free Radical Biology and Medicine. 2017;**111**:110-126

[114] Mashima R, Maekawa M. Lipid biomarkers for the peroxisomal and lysosomal disorders: Their formation, metabolism and measurement. Biomarkers in Medicine. 2018;**12**(1):83-95

[115] Li Q-Q et al. 12/15 lipoxygenase: A crucial enzyme in diverse types of cell death. Neurochemistry International. 2018;**118**:34-41

[116] Sbodio JI, Snyder SH, Paul BD. Redox mechanisms in neurodegeneration: From disease

outcomes to therapeutic opportunities. Antioxidants & Redox Signaling. 2018. DOI: ORG/10.1089/ARS.2017.7321. (Article in press)

[117] Truong VL, Jun M, Jeong WS. Role of resveratrol in regulation of cellular defense systems against oxidative stress. BioFactors. 2018;**44**(1):36-49

[118] Maher P. Potentiation of glutathione loss and nerve cell death by the transition metals iron and copper: Implications for age-related neurodegenerative diseases. Free Radical Biology and Medicine. 2018;**115**:92-104

[119] Borchert A et al. Crystal structure and functional characterization of selenocysteine-containing glutathione peroxidase 4 suggests an alternative mechanism of peroxide reduction. Biochimica et Biophysica Acta (BBA)-Molecular and Cell Biology of Lipids. 2018;**1863**(9):1095-1107

[120] Lenardão EJ, Santi C, Sancineto L. Bioactive organo selenium compounds and therapeutic perspectives. In: New Frontiers in Organoselenium Compounds. Switzerland: Springer; 2018. ISBN(P): 978-3-319-92404-5