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Focused review

Insights on alpha lipoic and dihydrolipoic acids as promising scavengers of oxidative stress and possible chelators in mercury toxicology

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ABSTRACT

Alpha lipoic acid (α-LA) and its reduced form dihydrolipoic acid (DHLA) have been historically considered as excellent anti-oxidants and oxidative stress scavengers. Upon oxidation with reactive oxygen species (ROS) and pro-oxidants, α-LA may be reconstituted from DHLA and other reduced forms. Oxidative stress is one of the fundamental causes of functional degeneration, autophagy and apoptosis leading to cytotoxicity and loss of cell survival, often due to exposure to xenobiotics, pollutants, heavy metals, and other environmental and endogenous toxicants. α-LA and DHLA can react with these molecules to strengthen the primary antioxidant defense system during cell injury. The compound α-LA is suggested for heavy metal detoxification, in particular for supporting the mercury (Hg) detoxifying process. Mercury is one of the major environmental toxicant, particularly noxious even upon limited exposure. Oxidative stress pathways have been identified as a key upstream event for Hg-induced toxicity in humans and animals. However, very few existing drugs to date can successfully prevent or reduce Hg toxicity. Although several thiol-based chelators, such as British Anti-Lewisite (2,3-dimercaptopropanol, BAL), meso-2,3-dimercaptosuccinic acid (DMSA), and sodium 2,3-dimercapto-1-propanesulfonate (DMPS), have shown promise for ameliorating Hg intoxication. In this review, the potential role of α-LA and DHLA in scavenging toxic metals and other xenobiotics is discussed, focusing especially on the mechanisms of actions of α-LA and DHLA as potential antioxidants towards Hg-induced toxicity.

1. Introduction

Metal and xenobiotics-derived toxicology still represent a huge and urgent problem in environmental science and medicine. Limited recent literature in the field highlighted the protective role of natural chelators, particularly focusing on alpha lipoic acid (α-LA) and its reduced form dihydrolipoic acid (DHLA) in environmental toxicology and related functional disorders in humans [1–3]. The chemical structure of α-LA and DHLA is shown in Fig. 1 and the molecular model of α-LA is shown in Fig. 2. The commonest perspective is that natural anti-oxidants are still widely acknowledged molecules, which would help cells to counteract metal toxicity and associated oxidative stress, thereby protecting cells from damage caused by xenobiotics, chemical pollutants, and heavy metals [4–7]. Moreover, very few data were published about the ability of these natural chelators to reduce possible damage caused by mercury (Hg). Researchers are aware that stressors are continuously produced fundamentally from mitochondria and endoplasmic reticulum, representing complex machinery that is finely tuned also by the same reactive oxygen species (ROS), acting as signaling molecules [8]. The antioxidant property of α-LA has been reviewed in the past, yet its role in human physiology has come in the spotlight particularly in recent years as a fundamental cofactor (nutrient supplementation or nutraceutical) to prevent degenerative disorders caused by metals intoxication [9–12].

This may suggest why α-LA has been widely used as an antioxidant compound in many multivitamin formulations, food supplements, anti-aging formulas, and even in human and pet food recipes [13,14]. Alpha-LA and its reduced form DHLA gained much interest due to their

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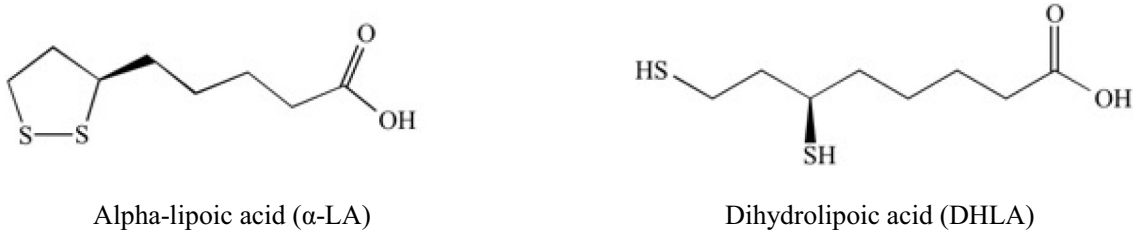

Alpha-lipoic acid (α-LA) Dihydrolipoic acid (DHLA)

Fig. 1. The chemical structures of alpha lipoic acid and its reduced form dihydrolipoic acid.

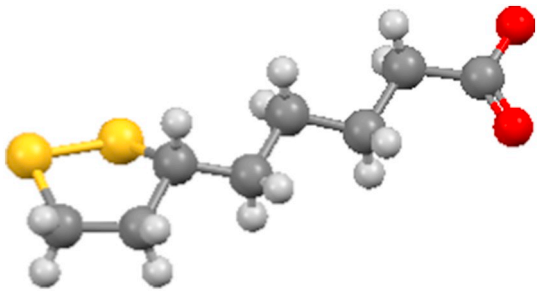

Fig. 2. Molecular structure of lipoic acid.
The coordinates were obtained from the Cambridge Structural Database, and the image was created using the software Mercury 3.5.

potential role in the chelation of metals and in restoring normal levels of intracellular glutathione (GSH) after depletion caused by toxicants, environmental pollutants or senescence [13,15,16]. A common concept about metal detoxification is that these pollutants can undergo clearance by physiological stressor scavenging [17].

Previous reports showed that α-LA possesses functional pleiotropism with different signal transduction pathways, the dysfunction of which leads to various pathologies. Therefore the use of α-LA as a potential therapeutic agent could appear promising for medical therapy and prevention [16,18,19]. In particular, a recent study showed that α-LA is capable of efficiently scavenging free radicals in vivo [20]. In its reduced form, DHLA can scavenge reactive free radicals via hydrogen transfer mechanism [20]. Furthermore, it keeps GSH and protein thiols in their reduced chemical forms [20]. In adrenocorticotropic hormone (ACTH)- or dexamethasone-induced hypertension in rats, α-LA could prevent hypertension from acting on mitochondria but not directly on the mitochondrial superoxide reduction [21]. This evidence suggests that the antioxidant activity of α-LA is not merely limited to the induction of the anti-oxidant enzymatic endowment of the cell, but it could participate in the complex machinery involving mitochondria and endoplasmic reticulum (ER) [8].

α–LA, which can pass through the blood-brain barrier (BBB) [22–24] is less active than DHLA in reducing the oxidation of ascorbate mediated by Fe^{3+}-citrate, probably because iron binding requires reduced thiols. Also, DHLA reduces, in a dose-dependent manner, the Cu^{2+}(histidine)(2)-mediated ascorbate oxidation [25]. The functional capacity of DHLA appears stronger than α-LA, at least in the interaction with transition metal ions. However, its beneficial properties have been recently debated by some controversial results indicating that DHLA can also act as a cancer promotor under certain conditions [26], presumably when combined with tamoxifen [27]. Therefore, the cellular context where DHLA operates is particularly important [28].

From a biochemical point of view, α-LA acts as a protector against alterations caused by oxidative stress initiated by heavy metals or toxic drugs [29,30]. Its ability to interact with the IRP2/IRE pathway, modulating iron signaling, leads α-LA to reduce iron deposition in the *substantia nigra*, thereby presumably inhibiting the progression of Parkinson's disease [31]. The interactions of α-LA with transition metals is particularly complex because the ability of α-LA to behave as a suitable scavenger often occurs in a complex synergism with essential trace elements [32].

Mercury is one of the most toxic environmental compounds, and it is of particular interest that α-LA and DHLA have been shown to possess chelating properties towards Hg^{2+} when used in an appropriate manner [33]. Mercury has been listed as the third most hazardous substance after arsenic (As) (1st) and lead (Pb) (2nd), by the Agency for Toxic Substances and Disease Registry (ATSDR) of the U.S. Department of Health and Human Services, and also as the most toxic substance in the United States. The model used by these Agencies and Expert Committees in their assessments takes into account the distribution of toxic substances in different geographical areas, also considering any toxicology pattern and toxic potential for human exposure at National Priorities Listed (NPL) sites [34,35].

The role of α-LA as a scavenger and anti-toxicant of Hg in humans dates back several years [36–38]. A possible hypothesis on this anti-toxicant mechanism may come from the role also exerted by vitamin C, buthionine sulfoximine, GSH and sodium 2,3-dimercapto-1-propanesulfonate (DMPS) in drastically reducing Hg-mediated nephrotoxicity and Hg levels in the liver, renal cortex, and urine of Wistar rats [39]. Lipoic acid showed promise in the reduction of Hg intake from Caco-2 cells [40]. Furthermore, α-LA can also act on the ability, shown by selenite to inhibit Hg toxicity. Selenite is an antagonist of Hg toxicity via the targetting of the selenoenzyme thioredoxin reductase, by which it can detach Hg from its binding with thiol groups in enzymes, an action also held by α-LA [41].

The toxicology of Hg is widely known [42–44]. The aim of the present review is to report new evidence about the use of α-LA in preventing and reducing Hg toxicity and to highlight the major toxicological and environmental concerns associated with Hg and transition metals. In this review, we will primarily attempt to address the detoxifying property of α-LA and DHLA in Hg toxicity.

2. Insights on α-LA and DHLA as radical scavengers and enzymatic cofactors

2.1. Metal chelating activity of α-lipoic acid and its derivatives compared to other chelating agents

Alpha-lipoic acid is widely considered an anti-oxidant and chelating agent in association with some vitamins, *N*-acetyl-cysteine (NAC), taurine, and liposomal GSH [45–47]. As a metal chelating agent, α-LA appeared in scientific papers very early, as a possible chelating agent of arsenic [48]. In more recent years, researchers have examined whether thioctic acid, then renamed as lipoic acid, actually exhibited the ability to chelate trace metals in biological tissues. Some paper reported that this compound formed a lipophilic complex with bivalent copper (Cu^{2+}) and inhibited Cu^{2+} mediated liposomal peroxidation [49]. In combination with a thiol chelator, α-LA resulted was shown to be a good candidate for preventing lead (Pb)-mediated poisoning [50]. The anti-oxidant property of α-LA, likewise glutathione (GSH), is considered a major hallmark for metal detoxifying activity, including Hg toxicity [38]. This anti-toxicant scavenging activity is also demonstrated in toxic organic molecules, such as formaldehyde [51]. This scavenging

capability can be achieved by the anti-oxidant ability of this natural compound, which is usually found in tomatoes, spinach, broccoli, Brussels sprouts, peas, and also visceral meats [52], to restore oxidized GSH [53,54]. Current research on natural products ability to chelate metals appears as a promising field of research; for example, polyphenols are possible agents for copper chelation [55]. Cysteine and methionine are reported as suitable chelators of iron and copper [56], and, in more general research on metal toxicology, chelation reactions are of the utmost importance [57]. In this perspective, α-LA can be considered only one of the increasing number of natural detoxifying molecules able to help advance the treatment of metal toxicity.

A few chemical studies considered the interaction of British Anti-Lewisite (BAL), *meso* 2,3-dimercaptosuccinic acid (DMSA) and dithiol, sodium 2,3-dimercaptopropane 1-sulfonate (DMPS) with Hg^{2+}. Some of these studies also come from past research. For example, Casas and Jones determined the complex formation constants for Hg^{2+} complexes with D,L-penicillamine, N-Acetyl-D,L-penicillamine, DMPS, and BAL using a titration procedure involving simultaneous measurements with a glass and a Hg electrode [58]. The stability constants obtained in this manner were of the order of 10^{-35}–10^{-44}. Chelating agents with two sulfhydryl groups give complexes whose $k\sim$ values are greater by a factor of 10^{7} than those that contain a single sulfhydryl group.

George et al. investigated the interaction of mercuric ions with DMSA and DMPS by a combination of mercury L_{III}-edge X-ray absorption spectroscopy and density functional theory calculations [59]. According to these authors, neither DMSA nor DMPS forms a true chelate ring structure with mercuric ions, and these drugs should be considered suboptimal for their clinical task in binding mercuric ions [59].

Chekmeneva et al. investigated the complexation of α-LA and DHLA with Hg^{2+}. Main complexes were both 1:1 Hg:α-LA and Hg:DHLA, although the formation of 1:2 complexes was also gained. α-LA and DHLA show different Hg^{2+} binding patterns at different pH-values [60,61]. The antidotal effects against organic Hg of a combination of α-LA with DMSA deserve to further investigation. A possible structure of the dinuclear $Hg_2(DHLA)_2$ is presented in Fig. 3.

2.2. The relationship between reactive oxygen species and mercury. A background

The potential of α-LA to counteract Hg toxicity is fundamentally associated with the ability of cells to activate their stress responsive machinery [38]. It is widely known that in homeostatic conditions, small quantities of ROS in the form of superoxide ($O_2\cdot^-$), hydrogen peroxide (H_2O_2), as well as hydroxyl radical (·OH), are commonly produced during oxygen metabolism, which mainly occurs in functional mitochondria [62,63]. Oxidative stress, which is, in a quite simplified version, a massive increase of ROS production, usually occurs during mitochondria functional imbalance, endoplasmic reticulum stress (ER-stress), unfolded protein response (UPR), impairment in proteasome function and disorder in peroxisomes-modulated autophagy. Such imbalance is usually elicited by stressors such as xenobiotics or metals [64–69]. Fundamentally, ROS are produced by the mitochondria redox chains and the use of oxygen [70]. Mitochondrial electron transport chain and oxidase enzymes including the NADPH oxidases, xanthine oxidase, lipoxygenases, cyclooxygenases, cytochrome P450 enzymes, and uncoupled nitric oxide synthases (NOSs) are considered primary endogenous sources of ROS [71]. In this functional scenario, Hg can easily impair many physiological activities. For example, organic Hg (methylmercury (MeHg)) can induce apoptosis via the ROS-mediated ER-stress [72].

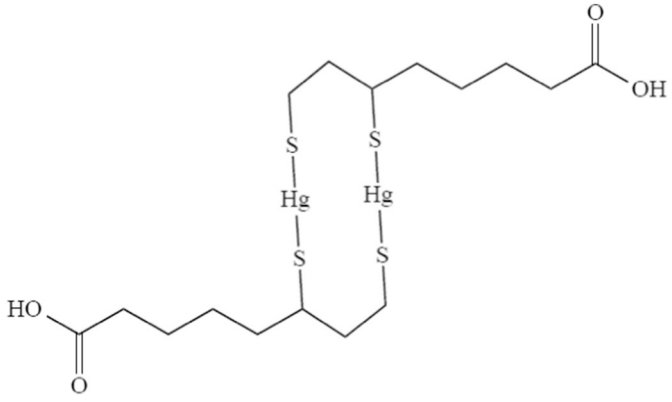

Fig. 3. A possible chemical structure of the complex between DHLA and Hg^{2+}, based on the considerations in the International System.

Mercury derived compounds that penetrate brain cells are presumed to initiate ROS production and induce neuroinflammation related to autism spectrum disorder, and in this sense, detoxifying processes are of the utmost importance in medicine [73–75].

Oxidative stress causes swelling and decoupling of the mitochondria and decreased ATP levels in the cell, also releasing factors involved in the cellular signal mechanisms for programmed cell death and apoptosis. Upon ATP deficiency, cell death takes the form of necrosis [76,77]. In mitochondria and other cellular constituents, oxidative stress may participate in exacerbating metal toxicity including Hg-toxicity [78].

Possible sources, absorption nature, pharmacokinetics and metabolic fates of Hg compounds are presented in Table 1. Mercury exposure in humans may include both inorganic and organic Hg derivatives. Organic Hg exposure occurs either from consumption of seafood as $MeHg^+$ or from the use of preservatives contained in medical products which are rapidly metabolized to ethylmercury (EtHg). EtHg and MeHg interact with thiols in enzymes and can pass across the blood-brain barrier causing deposition in brain cells [79]. Elemental mercury vapor (Hg^0) is easily absorbed via inhalation. A cubic meter of air can hold 20 mg of Hg at saturation at 25 °C. The daily respired volume of air is about 15–20 m^3, so a worker staying 8 h in a place saturated by Hg inhales from 100 to 135 mg of this toxic element [80].

Mercury is a component of dental amalgams that are still used by dentists in large parts of the world [81]. After uptake, elemental Hg rapidly crosses the blood-brain barrier and is converted to ionic Hg^{2+} intracellularly and retained in brain cells. Several studies have reported that the cationic Hg, both Hg^{2+}, and $MeHg^+$, has a strong affinity for protective nucleophiles, such as –SH and –SeH [82,83]. Therefore, they can target critical thiol- and selenol-molecules with antioxidant properties such as the GSH/glutathione peroxidase (GPx) enzyme complex [78] and thus may increase oxidative stress. Because of Hg affinity for thiol groups, organic Hg molecules can affect essential enzymes such as the mitochondrial pyruvate dehydrogenase as well as structural components in the neuronal cytoskeleton [84]. Although the brain is the major targeted organ of both organic and elemental Hg, Hg exposure can contribute to the pathogenesis of a variety of other diseases including hypertension, coronary heart disease, myocardial infarction, cardiac arrhythmias, generalized atherosclerosis, and renal dysfunction [85–87]. A relationship has been reported between MeHg exposure, glutamate action, calcium dyshomeostasis, and oxidative stress [78,88]. The relationship between Hg and oxidative stress is of fundamental importance enabling the scavenging of Hg toxicants by α-LA. The relationship between Hg toxicology and ROS-induced damage is particularly stressed in the literature [89–91]. This encouraged many researchers to focus on the role of ROS scavengers to prevent Hg toxicity, which can also affect enzymatic and hormonal pathway regulating further physiological mechanisms, such as blood pressure [92,93], and thereby causing cardiovascular and other systemic disorders.

2.3. Alpha lipoic and dihydrolipoic acids as antioxidants. The involvement of thiol radicals and some controversial activity

α-LA and DHLA react with different free radicals [94,95], which are

Table 1
Mercury: Sources, absorption, and metabolic fates.

	Methylmercury	Inorganic mercury	Organic mercury Ethylmercury
Source	Fish, poultry, pesticides	Dental amalgams, fossil fuels, old latex paint, thermometers, incinerators, occupational	Demethylation of methylmercury by intestinal microflora; biological oxidation of elemental mercury
Absorption	95–100% in the intestinal tract; 100 percent of inhaled vapor	75–85% of vapor absorbed	7–15% of the ingested dose is absorbed; 2–3 percent of dermal dose absorbed in animals
Distribution	Lipophilic, distributed throughout the body; readily crosses blood-brain barrier and placental barrier; accumulates in the brain and kidney	Lipophilic, distributed throughout the body; crosses blood-brain and placental barriers; accumulates in the brain and kidney	Does not cross the blood-brain or placental barrier; found in the brain of neonates; accumulates in the kidneys
Metabolism	Cysteine complex necessary for intracellular absorption; slowly demethylated to inorganic mercury in the brain by tissue macrophages, fetal liver, and free radicals	Oxidized intracellularly to inorganic mercury by catalase and hydrogen peroxide	Methylated by intestinal microflora; binds and induces metallothionein biosynthesis
Excretion	90% in bile, feces; 10% in urine	Urine, feces, sweat, and saliva	Urine, bile, feces, sweat, and saliva
Toxicity	Demethylation to inorganic (divalent) mercury; free radical generation; binding to thiols in enzymes and structural proteins	Oxidation of inorganic (divalent) mercury	Binding to thiols in enzymes and structural proteins

characterized by having an unpaired electron or by rapidly producing unstable and extremely reactive species. The resulting thiol radicals are very short-lived species and therefore difficult to detect, although confirming observations have been performed with electron spin resonance [96]. Thiol radicals can react with DHLA radicals, reshaping α-LA and DHLA. These radicals are particularly involved in ROS homeostasis and ROS signaling [97–99]. Much more important are protein thyil radicals, which are major intermediates, generated in redox processes of thiols and disulfides [100]. Oxidative stress, with its production of ROS and reactive nitrogen species (RNS), can indirectly regulate their homeostasis, by activating AMPK [101,102].

Reduced GSH is the primary antioxidant to react with free radicals and is found intracellularly at millimolar concentrations. Lipoic acid radicals can be eliminated by reacting with GSH [103]. α-LA contributes to restoring functionality as antioxidants of ascorbate (vitamin C), vitamin E, and GSH [104,105]. A potential mechanism is shown schematically in Fig. 4. In HepG2 cells, α-LA was reported to regenerate GSH via the Nrf2/ARE signaling pathway and thus alleviate cadmium (Cd)-induced cell toxicity [106,107]. Macias-Barragan et al. have reported a similar de novo synthesis and recycling pathway used by Cd and α-LA to balance GSH in HepG2 cells [108]. Furthermore, α-LA regulates numerous signal transduction pathways that are highly susceptible to oxidative stress such as nuclear factor erythroid 2-related factor (Nrf2) [109]. This would also suggest a role for GSH/oxidized glutathione (GSSG), whose default redox potential −0.24 V is higher than that of α-LA/DHLA (−0.32 V) so that DHLA can directly reduce GSSG.

Even though α-LA and DHLA have proven to be excellent antioxidants, pro-oxidant effects of α-LA and DHLA have also been observed under special circumstances, leading to peroxidation of lipids [110–112]. This controversial effect depends on the particular cellular condition in which ROS exert their signaling activity, rather than a damaging effect. Taken these issues into account, α-LA and DHLA still behave as anti-oxidant compounds. Bhatti et al. reported that α-LA has anti-oxidant effects on streptozotocin-induced diabetic rats as it attenuated albuminuria, glomerulosclerosis, tubulointerstitial fibrosis, superoxide (O_2^-) anion generation, and kidney expression of the NADPH oxidase subunits p22phox and p47phox [109]. However, in non-diabetic rats, α-LA was reported to show pro-oxidant effects by reversing oxidative stress factors such as increased superoxide anion generation and NADPH oxidase subunits p22phox and p47phox expression in the kidney [109].

Cakatay et al. reported pro-oxidant effects of α-LA by investigating protein oxidation parameters, such as protein carbonyl (PCO), nitrotyrosine (NT), advanced oxidation protein products (AOPP), and protein thiol (P-SH), as well as oxidative stress parameters such as total thiol (T-SH), non-protein thiol (Np-SH), and lipid hydroperoxide (LHP) in the heart muscle tissue of aged rats with α-LA supplementation (100 mg/kg body wt/day) [112]. Except for P-SH, Np-SH, and LHP, further tested markers were found at increased levels in the heart muscle tissue of α-LA -treated aging rats [112]. In recent years, Silvestri and colleagues reported very interesting findings. They showed a slight pro-oxidant effect of α-LA and coenzyme Q10 with no damage to DNA [113]. In their study, they tested whether oral supplementation with 200 mg/day of coenzyme Q10 alone or in association with 200 mg/day of α-LA for 15 days on 16 healthy subjects, was effective. It was reported that both compounds produced antioxidant and bioenergetic effects, thus improving the oxidative status of the lipid compartment and mitochondrial functionality in peripheral blood lymphocytes. Concomitantly, an increased intracellular ROS level was observed, although it did not lead to enhanced DNA oxidative damage [113].

Pro-oxidant activity of flavonoids and natural compounds must be considered as eliciting ROS-signaling, and ROS are important signals for SOD activity and the same stress response [114–118]. Nur et al.

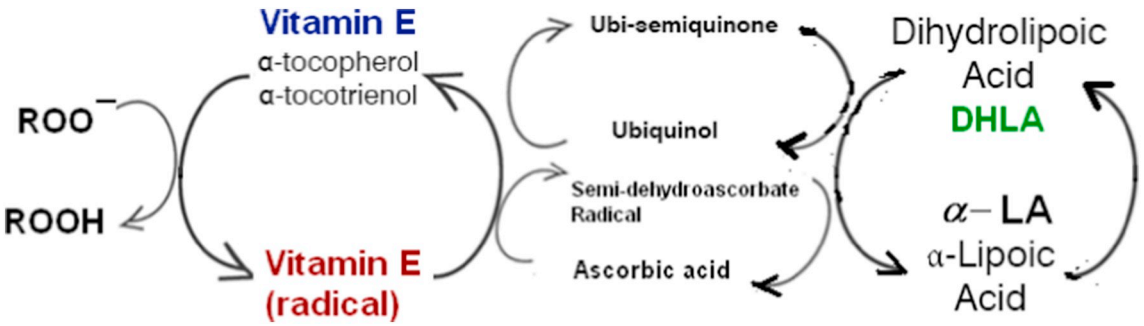

Fig. 4. Involvement of alpha lipoic acid (α-LA) and dihydrolipoic acid (DHLA) in the regeneration of vitamin C and E adapted with an update from Biewenga et al. [90].

reported a pro-oxidant effect of α-LA in combination with cisplatin to modulate apoptosis and oxidative stress in MCF-7 breast cancer cells [111]. In their study, they found an increased level of apoptosis, mitochondrial membrane depolarization, ROS production, lipid peroxidation, poly-(ADP)-ribose polymerase 1 (PARP1), caspase 3 and 9 expression levels in simultaneous α-LA (0.05 mM) and cisplatin (0.025 mM)-treated MCF-7 cells. Although cell viability, reduced GSH, and glutathione peroxidase (GPx) values were decreased by the treatments [111]. They proposed that activation of the transient receptor potential cation channel subtype V1 (TRPV1) increased apoptosis and oxidant effects of cisplatin, but its action on the values was further increased by the α-LA treatment [111].

Further research showed that α-LA and DHLA enhanced the mitochondrial permeability transition (MPT) [119]. α-LA was reported to increase glucose uptake by 3T3-L1 adipocytes via elevating intracellular oxidant levels and/or facilitating insulin receptor autophosphorylation presumably by oxidation of critical thiol groups present in the insulin receptor β-subunit [110,120–122].

3. Role of α-LA as a detoxifying and anti-oxidant molecule

Despite the many, somewhat conflicting hypotheses on the role of α-LA and its reduced form, its role is fundamentally similar to the many natural phenolic compounds able to trigger the optimal stress response in cells. Its activity in Hg scavenging appears to be encouraging. This comes from α-LA's role in protecting cells from heavy metal and transition metal toxicity [123,124]. Interestingly, low doses of Cd promote α-LA's ability to activate Nfr2 in GSH production [125]. This does not seem to occur with Hg, suggesting that Hg is more hazardous than Cd [126]. The activity of α-LA against the Hg toxicity is not widely published; unfortunately, due to difficulties in investigating these issues clinically. Current insights on its role as anti-oxidant and natural chelator appear promising with regard to its suitability in scavenging metal pollutants, including Hg.

As previously described in this paper, the administration of α-LA has been shown to reduce oxidative stress and to restore the level of antioxidants in various physiological and pathophysiological states [9,127]. Thus, in humans, a reduction in peroxidation of LDL following α-LA uptake has been reported [128]. Lipid peroxidation during sport-induced oxidative stress also decreased while GSH levels increased in the blood and liver [129]. The effect on Hg toxicology is of particular interest [130,131]. Alterations to the oxidative stress response are caused by an increase in thiol-groups availability including the availability of reduced GSH [132,133]. Therefore, it is conceivable that α-LA may counteract the toxic effect of Hg. As an anti-oxidant, α-LA must also play a significant role in Hg-mediated oxidative stress [38]. However, although α-LA has been successfully used in As toxicity, via a synergistic effect with DMSA in rats [134], its ability to decrease kidney or brain levels of Hg showed some conflicting evidence [135].

A further effect of oxidative stress is ROS-mediated damage in senescence. Aging is accompanied by deteriorations of DNA, lipids, and proteins in various tissues such as muscle and brain. In a small scale, randomized placebo controlled-trial study on Alzheimer's disease (AD) treatment using omega-3 fatty acid along with α-LA slowed down the cognitive and functional decline in mild to moderate participants over 12 months' period [9]. Damage to the mitochondrial DNA may result in reduced cell respiration and ATP synthesis [136,137]. The role of Hg exposure in aging has not been addressed to date. Some evidence, showing the ability of α-LA in preventing age-related neurodegeneration also caused by Hg-mediated oxidative stress [138] has been published.

Administrating α-LA and DHLA in animal experiments also had positive effects on tissue damage caused by oxidative processes such as cataracts in diabetes [139–141], liver disease [127], neuronal diseases [142,143], and heart diseases [144,145]. α-LA also reduced lipid peroxidation in the kidneys caused by the anticancer drug cisplatin, and restored the level of decreased antioxidant enzymes in rats; a role recently reappraised for breast tumors [118]. Recent studies also reported evidence about the potential therapeutic application of α-LA against colorectal cancer cells (CRC) [146], MFC-7 [147], H460 human lung cancer cells [148], and HepG2 [149] through different signal transduction pathways. It has also been reported that α-LA enhances the functions of various anticancer drugs such as 5-fluorouracil in CRC [146] and cisplatin in MCF-7 cells [118].

Furthermore, α-LA also induces apoptosis in different cancer cells [146]. Interestingly, α-LA does not necessarily always follow the oxidative stress pathway. It did not affect the reactive oxygen species (ROS) status while making synergism with 5-fluorouracil (5-FU) in colon cancer cells (CRCs) [146]. Interestingly, Hg may induce neurodegeneration by targeting Janus kinase (JAK), which is a component of a fundamental signaling pathway, i.e., the JAK-signal transducer and activator of transcription (JAK-STAT) pathway, in cancer [150–152]. Actually, the ability of antioxidants including α-LA to reduce Hg levels in tissues greatly depends on the level of Hg and the detoxifying enzymatic systems. Fundamentally, low doses of organic and inorganic Hg, most probably do not interact with the oxidative stress machinery despite targeting important signaling pathways [153].

In addition, to inhibiting pro-oxidant damage and enhancing antioxidant capacity, the α-LA administration may also result in further benefits. α-LA was shown to lower the blood glucose levels in patients with type 2 diabetes [154,155]. This may be due to increased glucose uptake in cells by stimulation of insulin pathways via redox effects on the insulin receptor [156]. Mercury exposure has been recently associated with the risk of developing diabetes in later life [157].

Considering the effect of Hg-containing compounds on sulfur-containing antioxidants (*N*-acetyl-L-cysteine, α-LA, and GSH), it is reasonable that such exposure will decrease the cellular mechanisms of oxidant defense and thus increases oxidative stress.

A range of agents has been used for the treatment of Hg toxicity including minerals (zinc and selenium), endogenous thiols (*N*-acetylcysteine, GSH), synthetic dithiols (DMPS, DMSA, and endogenous disulfide (α-LA)). The role of α-LA and DHLA in the treatment of Hg toxicity, in particular, the neurological and developmental deficits precipitated by exposure to mercurials, has been extensively discussed in previous reports [158,159]. ROS are reported to be involved in the MeHg-induced neurotoxicity in different experimental models [160–162]. The available chelating agents, such as DMSA and DMPS, have limited ability to counteract the MeHg neurotoxicity [163,164]. Scientists are looking for drugs that are more effective in counteracting Hg neurotoxicity or drug combinations for the treatment of MeHg neurotoxicity [165].

Interestingly, α-LA has been shown to regulate the release of GSH into bile secretions [134]. In past studies, a significant increase of GSH in bile was reported to induce a drastic elevation of inorganic Hg [166]. A moderate dose of lipoic acid resulted in a substantially increased biliary excretion of MeHg [134]. Yang et al. studied the potential of α-LA as a pretreatment to inhibit MeHg-induced neurotoxicity in rat cerebral cortex [167]. In their study, they report ameliorated effects of a moderate dose of α-LA on MeHg induced oxidative stress in the cerebral cortex of rats. Furthermore, they provided a clue about the possible relationship between oxidative stress and glutamate metabolism/transport disorders [168].

In a previously reported study on 64 rats, either treated with MeHg alone or pretreated with α-LA [135], a significant inhibition of SOD and GPx accompanied by ROS generation, and neuronal damage was induced by MeHg alone, whereas pretreatment with α-LA at least partially reduced the MeHg-induced neuronal damage via antioxidant pathways. Moreover, the similar protective effects of α-LA were found via antioxidant pathways against MeHg-induced neuronal injury in primary cultured neurons [169]. Aposhian et al. tested the hypothesis that GSH, vitamin C, or lipoic acid alone or in combination with DMPS or DMSA would decrease brain deposits of inorganic Hg [135],

evidence-based upon original studies on rabbits [170]. To investigate the hypothesis, they exposed young rats to Hg^0 vapor for seven consecutive days. After exposure, the subjects were administered with DMPS, DMSA, GSH, vitamin C, lipoic acid given alone, or in combinations, given simultaneously. They found no significant additive effects of α-LA combined with DMPS or DMSA in alleviating the *inorganic* Hg concentration in rat brain [170].

4. Concluding remarks

Accumulating evidence in the literature indicates that α-LA and DHLA have antioxidant activity both in vitro and in vivo. However, the application of α-LA and DHLA is still not approved as they also induce some undesired effects. Nevertheless, according to the reviewed findings, it can be concluded that α-LA and DHLA have well-documented abilities to prevent oxidative stress, albeit the potential threat to act as a pro-oxidant. It has also been shown that α-LA and DHLA act through a variety of signaling pathways that might attract clinical interest and possibly pharmacological applications. α-LA has been reported to have a number of potentially beneficial effects in both prevention and treatment of peroxidative-related diseases. The selection of appropriate pharmacological doses of α-LA for use in such oxygen-related disorders is therefore particularly critical [110].

Of particular relevance is that several studies have indicated that α-LA and DHLA have a promising role in MeHg detoxification; many studies reported that these compounds can increase excretion of MeHg in bile, while DMSA increases the urinary excretion of this mercurial. α-LA and DHLA showed a potential antioxidant role in MeHg-induced oxidative stress. Considering all the promising factors reviewed regarding their anti-oxidative potentials, both α-LA and DHLA merit further careful investigations in experimental organisms and cellular models.

Acronyms

ACTH	adrenocorticotropic hormone
AMPK	adenosine monophosphate kinase
ARE	anti-oxidant responsive element
BAL	British Anti-Lewisite
DMSA	*meso* 2,3-dimercaptosuccinic acid
DMPS	dithiol, sodium 2,3-dimercaptopropane 1-sulfonate
ER	endoplasmic reticulum
LDL	low-density lipoproteins
NPL	National Priorities Listed
Nrf2	nuclear factor E2-related factor 2
p22phox	p47 phox components of the NADPH oxidase (protein 22 oxidase…)
SOD	superoxide dismutase
STAT	signal transducers and activators of transcription

Conflicts of interest

The authors declare no conflicts of interest.

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