Revista Brasileira de Farmacognosia (2023) 33:272–287
https://doi.org/10.1007/s43450-023-00370-1

REVIEW

Molecular and Therapeutic Insights of Alpha-Lipoic Acid as a Potential Molecule for Disease Prevention

Amit Kumar Tripathi[1,2] · Anup Kumar Ray[3] · Sunil Kumar Mishra[4] · Siddharth Mall Bishen[5] · Hirdyesh Mishra[5] · Aman Khurana[4]

Received: 16 October 2022 / Accepted: 25 January 2023 / Published online: 7 February 2023

Abstract

Alpha-lipoic acid is an organic, sulfate-based compound produced by plants, humans, and animals. As a potent antioxidant and a natural dithiol compound, it performs a crucial role in mitochondrial bioenergetic reactions. A healthy human body, on the other hand, can synthesize enough α-lipoic acid to scavenge reactive oxygen species and increase endogenous antioxidants; however, the amount of α-lipoic acid inside the body decreases significantly with age, resulting in endothelial dysfunction. Molecular orbital energy and spin density analysis indicate that the sulfhydryl (-SH) group of molecules has the greatest electron donating activity, which would be responsible for the antioxidant potential and free radical scavenging activity. α-Lipoic acid acts as a chelating agent for metal ions, a quenching agent for reactive oxygen species, and a reducing agent for the oxidized form of glutathione and vitamins C and E. α-Lipoic acid enantiomers and its reduced form have antioxidant, cognitive, cardiovascular, detoxifying, anti-aging, dietary supplement, anti-cancer, neuroprotective, antimicrobial, and anti-inflammatory properties. α-Lipoic acid has cytotoxic and antiproliferative effects on several cancers, including polycystic ovarian syndrome. It also has usefulness in the context of female and male infertility. Although α-lipoic acid has numerous clinical applications, the majority of them stem from its antioxidant properties; however, its bioavailability in its pure form is low (approximately 30%). However, nanoformulations have shown promise in this regard. The proton affinity and electron donating activity, as a redox-active agent, would be responsible for the antioxidant potential and free radical scavenging activity of the molecule. This review discusses the most recent clinical data on α-lipoic acid in the prevention, management, and treatment of a variety of diseases, including coronavirus disease 2019. Based on current evidence, the preclinical and clinical potential of this molecule is discussed.

Keywords Electronic structure study · Pharmacological potential · Gut microbiota · Molecular targets · Neuroprotection · Thioctic acid

Introduction

α-Lipoic acid, commonly known as thioctic acid (**1**; (–)-(*R*)-5-(1,2-dithiolan-3-yl) pentanoic acid), is usually found in mitochondria and is enormously important as for various metabolic enzymatic reaction (Reed et al. 1951). Being an organosulfur and biological antioxidant, α-lipoic acid is produced normally in plants, animals, and human beings forming covalent bonds with proteins and plays a vital role in the Krebs cycle. In the enzymatic complexes involved in metabolic reaction and generation of energy for the cells, α-lipoic acid acts as a cofactor (Brookes et al. 1983). α-Lipoic acid has one chiral center and exists as *R*- and *S*-enantiomeric forms with diverse beneficial health effects (Golbidi et al. 2011). The *R* isomer occurs naturally in food

✉ Sunil Kumar Mishra
skmishra.phe@iitbhu.ac.in

1 School of Basic and Applied Science, Galgotias University, Gautam Buddha Nagar, UP, Noida, India

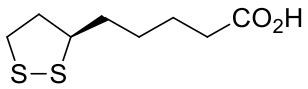
2 Molecular Biology Unit, Institute of Medical Science, Banaras Hindu University, Varanasi 221005, India

3 Department of Natural Products, National Institute of Pharmaceutical Education and Research, Sahibzada Ajit Singh Nagar, Punjab, India

4 Department of Pharmaceutical Engineering and Technology, Indian Institute of Technology, Banaras Hindu University, Varanasi 221005, India

5 Department of Physics, Banaras Hindu University, Mahila Maha Vidyalaya, Varanasi, India

sources, especially from meat and vegetables, whereas the *S* isomer is prepared through synthetic chemical reaction. Though naturally α-lipoic acid exists as the *R*-enantiomer (**1**), the synthetic supplementation consists of both *R* and *S* forms as a racemic mixture (Ghibu et al. 2009). Nevertheless, only *R*-α-lipoic acid conserves the lysine residues in an amide linkage in multi-enzyme complexes, such as pyruvate dehydrogenase, thus making this enantiomer fundamental as a cofactor in biological systems (Shay et al. 2009).



1

As a dietary supplements α-lipoic acid has become a common ingredient in regular products like anti-aging supplements and multivitamin formulations (Shay et al. 2009). The utilization of α-lipoic acid in dietary supplements is increasing due to its antioxidant and anti-diabetic properties (Lee et al. 2009). Along with that, it ameliorates age-related cognition, diabetes mellitus, cardiovascular and erectile dysfunction, neuromuscular loss, and cancer (Wollin and Jones 2003; Isenmann et al. 2020). In addition, it adjusts various signaling pathways of inflammation (Suh et al. 2004). α-Lipoic acid has multi-beneficial functions (Fig. 1); besides behaving as an enzymatic cofactor, it is involved in the metabolism of lipids and glucose and manages gene transcription. Heavy metals in bloodstream are responsible for oxidative stress but α-lipoic acid, being an eminent antioxidant, takes away the heavy metals from the bloodstream and prevents oxidative stress (Fig. 2). α-Lipoic acid differs from other antioxidants due to its amphipathic nature as a lipid and water-soluble compound. Regardless of its advancements as a strong antioxidant, the use of α-lipoic acid is prohibited for medicinal purposes due to its short half-life (t1/2) and low bioavailability (about 30%), which are responsible for its hepatic degradation, low solubility,

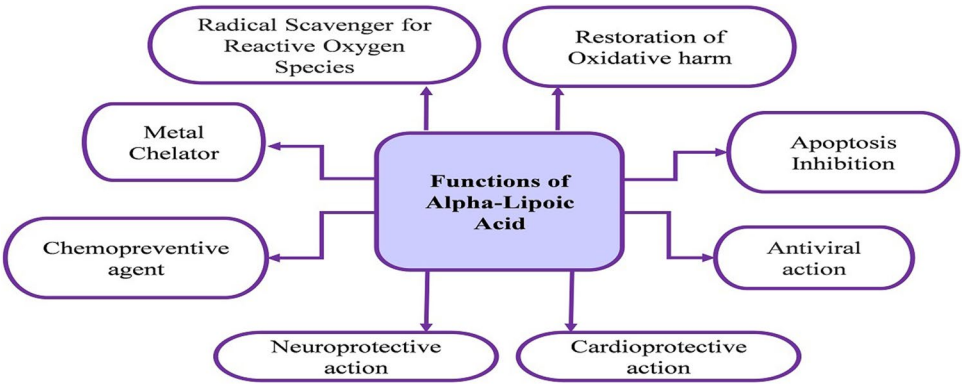


Fig. 1 Cellular and molecular functions of α-lipoic acid

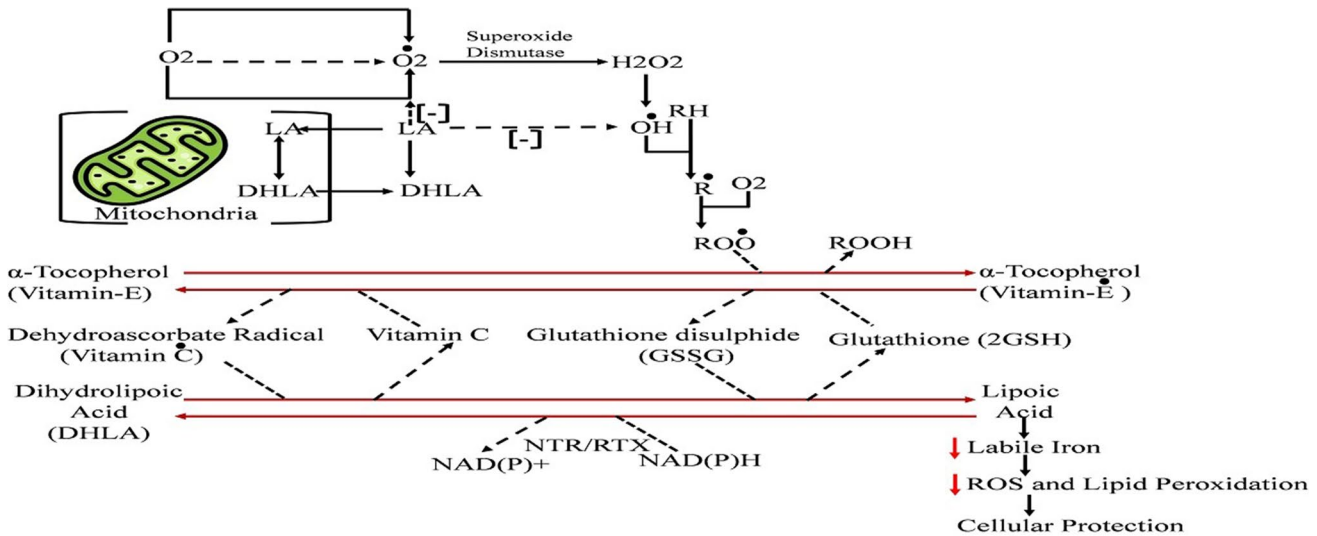


Fig. 2 Mechanism for antioxidant properties of α-lipoic acid

and instability in the gastrointestinal tract (Salehi et al. 2019). These limitations are the result of a reversible reduction/oxidation reaction of α-lipoic acid, as in vivo studies have demonstrated that α-lipoic acid is quickly reduced to dihydrolipoic acid by a hydrogenation and opening of the dithiolane ring and the emergence of a dithiol in the molecules, which is excreted from cells (Keith et al. 2012).

α-Lipoic acid biochemically interacts with many molecular targets (Fig. 3). Various cell culture and animal-based studies show that α-lipoic acid and dihydrolipoic acid chelate the redox-active metals. It was found that it is the property of the chelated metal that determines how α-lipoic acid and its reduced form bind with metal ions. Cell culture studies show that α-lipoic acid binds to Zn^{+2}, Cu^{+2}, and Pb^{+2}, but other studies show that α-lipoic acid cannot chelate ferric ions. Cell culture studies also provide facts that dihydrolipoic acid forms complexes with Pb^{+2}, Cu^{+2}, Hg^{+2} Zn^{+2}, and Fe^{3+} (Ou et al. 1995). Diabetes mellitus, hypertension, Alzheimer's disease, Down syndrome, cognitive dysfunction, and some types of cancer, including breast cancer, have all been shown to have multiple biological activities of α-lipoic acid (Wollin and Jones 2003). Up to now, the completed clinical trials are 167, in addition to 16 that are currently ongoing (Table S1).

Search Strategies

The information for this article was collected from clinicaltrials.gov, Google Scholar, Scihub, ScienceDirect, Springer Nature, and Pubmed with α-lipoic acid (**1**) as keyword. Pubchem was referred for structural studies. The content in this manuscript is from the 2000–2022 year and include the search terms alpha lipoic acid, COVID-19, Gut microbiota, cáncer, neurological disorder, phytochemical proerties, metabolic disease, neuroprtotective activities, inflammatory, antimicrobial, and Polycystic Ovarian Syndrome.

Discussion

Physicochemical Properties

The molecular weight of α-lipoic acid ($C_8H_{14}O_2S_2$) is 206.318 g/mol, and its melting point ranges from 60 to 62 °C. It is a solid, light yellow to yellow crystalline powder, and it has a half-life (t1/2) of 30 min to 1 h. It is an organosulfur compound derived from caprylic acid (octanoic acid). It is slightly soluble in methanol, chloroform, and DMSO. It should be stored in a cool, dark, and dry environment, at 0 °C for short-term storage (few days to weeks) and at − 20 °C for long-term storage (few months to years). The shelf life of α-lipoic acid is 3 years and is used for the manufacturing of several capsules. *R*-(+)-alpha-lipoic acid is one of the cofactors for mitochondrial enzymes and therefore plays a central role in energy metabolism. *R*-(+)-α-lipoic acid is unstable when exposed to low pH or heat, and therefore, it is difficult to use the enantiopure for in medicines. Both enantiomeric forms are produced in equal amounts during achiral manufacturating processes.

The dithiolane ring is accounted for the reactivity of α-lipoic acid. The redox couple created by α-lipoic acid and dihydrolipoic acid is very potent, having a redox potential of − 0.32 V, and the most powerful natural antioxidant. For example, this couple is a better antioxidant agent that similar biological sulfur-containing redox pairs as cystine/cysteine and glutathione and its oxidized state (GSH/GSSG) with

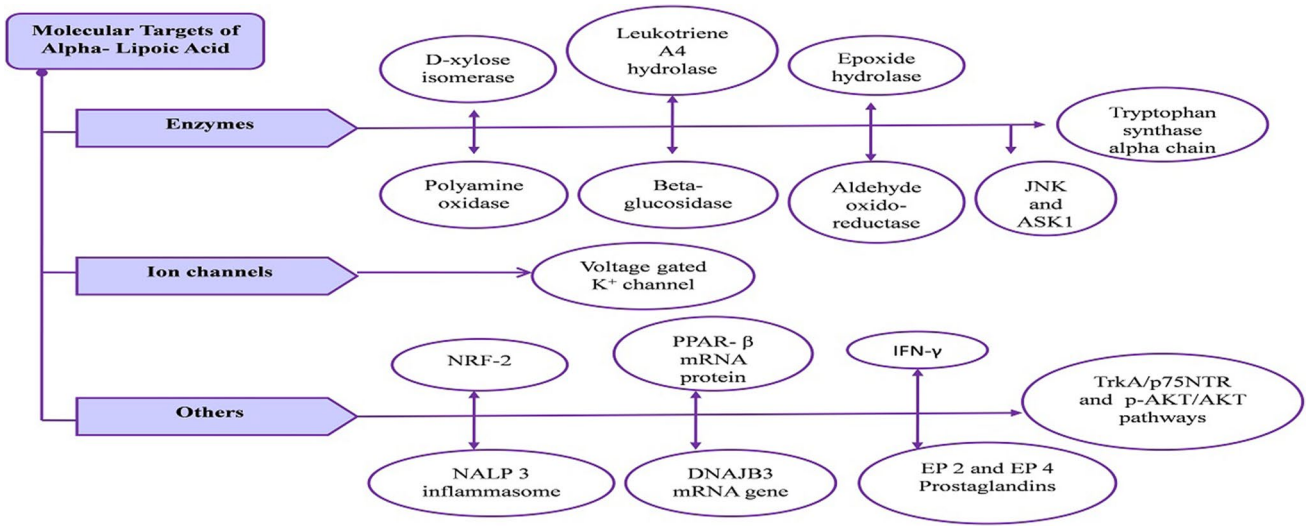


Fig. 3 Molecular targets of α-lipoic acid against various diseases

a redox potential of 0.24 and 0.22 V (Jocelyn 1967).There are certain facts available which show that α-lipoic acid and dihydrolipoic acid in combination can scavenge a diversity of reactive oxygen species, hydroxyl radicals, and hypochlorous acid (Shay et al. 2009).

Electronic Structure Study

The electronic structure study of the enantiomeric forms of α-lipoic acid has been done in the ground state using the DFT/B3LYP/6-31G (d,p) level of theory with Gaussian 09 suite of program. The theoretical results obtained from DFT calculations reveal that ground state energy for the *S*-enantiomer is 1260.1747 Hartrees, whereas for the *R*-form, ground state energy is 1260.1760 Hartrees. Therefore, the *R*-enantiomer seems to be relatively more stable than *S*-enantiomer by 0.82 kcal/mol. However, the energy difference is so small that both the isomers can be treated equivalent in energy.

The dipole moment can be understood in terms of charge separation within the molecule at a specific distance. It reflects the amount of molecular polarity developed at the end of the molecular dipole. For α-lipoic acid, the *R*-enantiomer with a polarity of 2.693 Debye is less polar than the *S*-enantiomer with a polarity of 4.289 Debye. So, one can expect more solubility for the *S*-enantiomer in polar solvents. Also, there is subtle change in the polarizability of the molecules (~ 139 a.u.). Polarizability is viewed as a relieve of distortion of atomic or molecular electronic charge cloud. Also, calculated molar specific heat for both the molecules is same (~ 48.7 cal/molK) at simulation temperature of 298.15 K and pressure of 1 atm.

Further, to understand the electronic charge distribution and the molecular electrostatic potential (MEP) in a molecule, Mulliken population analysis and MEP plot of all the three structures were carried out as tabulated in Table S2 and shown in Fig. 4. The MEP plot red being the negative extreme and blue being the positive extreme. As both the molecules are enantiomers of each other, there is not any significant change in the charge density. The carbonyl oxygen has a negative charge density and thus acts as the center for the electrophilic attack. The sulfur atoms possess positive charge density in *S*-α-lipoic acid, while slightly negative charge density in *R*-α-lipoic acid.

Deprotonation of the carboxylic acid gives a carboxylate anion (water soluble) in biological reactions. Carboxylic acids are polar. Because they are both hydrogen-bond acceptors (the carbonyl –C = O) and hydrogen-bond donors (the hydroxyl –OH), they also participate in hydrogen bonding. The acidity, combined with the ability to establish relatively strong electrostatic interactions and hydrogen bonds, is the reason this functional group is often a key determinant in drug–target interactions. However, despite the success of carboxylic acid drugs, the presence of a carboxylic acid residue in a drug or a drug candidate can represent a liability. For instance, a diminished ability to passively diffuse across biological membranes can raise a significant challenge, particularly in the context of central nervous system (CNS) drug discovery, where the blood–brain barrier (BBB) can be relatively impermeable to negatively charged carboxylate.

The HOMO is the highest occupied molecular orbital containing electronic charge, while LUMO is the lowest unoccupied molecular orbital with a deficit of electronic charge density (Gupta and Bhattacharjee 2019). HOMO–LUMO energy gap provides information about the radiation which the molecule will absorb. From the HOMO–LUMO plot of both α-lipoic acid enantiomers, it is very much clear that molecular orbitals of sulfur atoms play an important role in chemical reactions involving ground to excited state transitions. The high energy gap indicates that photochemical reaction would occur in near UV region. HOMO orbital

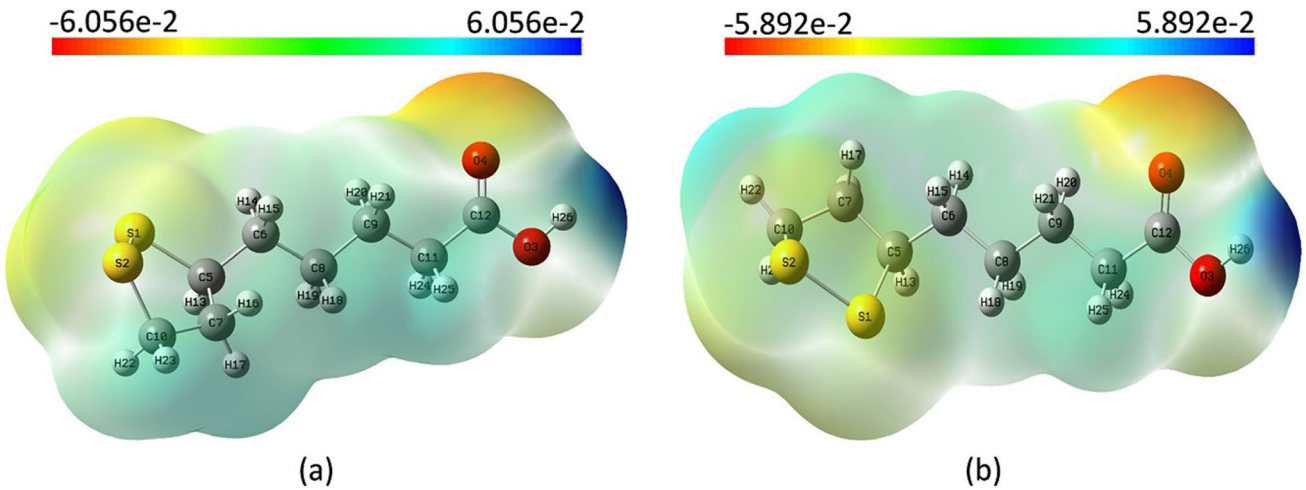


Fig. 4 Molecular electronic potential plots of the two enantiomers of α-lipoic acid. **a** *S*-α-lipoic; **b** *R*-α-lipoic acid, the biologically active isomer

energy and spin density distribution study of the molecule may be used for describing the free-radical scavenging activities. The molecule also contains acidic moiety in the structure with a tendency of proton donation and reduction activity. α-Lipoic acid is readily absorbed from the diet. It is undoubtedly rapidly converted to dihydrolipoic acid in many tissues. One or both components of the redox couple efficiently quench several free radicals in both lipid and aqueous cellular enviroments, such as superoxide radicals, hydroxyl radicals, hypochlorous acid, and peroxyl radicals (Packer et al.1995; Bingham et al. 2014)Re.

Remarkably, neither α-lipoic acid nor dihydrolipoic acid can scavenge hydrogen peroxide, possibly the most abundant second messenger ROS, in the absence of enzymatic catalysis. The following mechanisms of free-radical scavenging may be proposed for the α-lipoic acid/dihydrolipic acid redox couple:

Hydrogen atom transfer mechanism:

Hydrogen peroxide

$$RSH + X^{\bullet} \rightarrow RS^{\bullet} + XH$$

Proton loss electron transfer mechanism:

$$RS \rightarrow RS^{-} + H^{+}$$

$$RS^{-} + X + H^{+} \rightarrow RS + XH$$

Single electron transfer followed by proton transfer mechanism:

$$RSH + X \rightarrow RSH^{+} + X$$

$$RSH^{+} \rightarrow RS + H^{+}$$

Lipoic Acid Metabolism

Lipoic acid is an essential cofactor for mitochondrial metabolism and is synthesized de novo using intermediates from mitochondrial fatty acid synthesis type II, *S*-adenosylmethionine, and iron–sulfur clusters. This cofactor is required for catalysis by multiple mitochondrial 2-ketoacid dehydrogenase complexes, including pyruvate dehydrogenase, α-ketoglutarate dehydrogenase, and branched-chain keto acid dehydrogenase. α-Lipoic acid also plays a critical role in stabilizing and regulating these multi-enzyme complexes. Many of these dehydrogenases are regulated by reactive oxygen species, mediated through the disulfide bond of the prosthetic lipoyl moiety. Collectively, its functions explain why α-lipoic acid is required for cell growth, mitochondrial activity, and coordination of fuel metabolism (Solmonson and DeBerardinis 2018).

With t_{max} values between 10 and 45 min, α-lipoic acid absorbs swiftly. It is also promptly removed, with a mean plasma elimination half-life of 0.56 h. α-Lipoic acid (20%) was typically excreted as a non-conjugated compound.

Exogenous racemic mixture of α-lipoic acid is orally administered for therapeutic treatment of diabetic polyneuropathy and demonstrated that completely absorbed by gastrointestinal tract and limited absolute bioavailability by hepatic extraction. The racemic misture of α-lipoic acid (600 mg) administered daily in 9 healthy volunteers and observed the metabolites *S*-methylated β-oxidation products (4,6-bismethylthio-hexanoic acid and 2,4-bismethylthio-butanoic acid) confirmed by HPLC-electrochemical assay (Teichert et al. 2003).

Pharmacological Action

Cytotoxic Actvity

Several studies have provided facts that acts as a biological antioxidant and plays a leading function in cellular growth due to its ability to scavenge reactive oxygen species and renew endogenous antioxidants (Attia et al. 2020), contributing to α-lipoic acid-dependent cell death in various types of cancer like breast cancer, lung cancer, and colorectal cancer intimating that the mitochondrial apoptotic pathway is triggered by α-lipoic acid, also various researches show that α-lipoic acid plays a significant role in cancers related to metabolism (Dozio et al. 2010; Choi et al. 2012; Trivedi and Jena 2013; Omran and Omer 2015; Attia et al. 2020; Yadav et al. 2022a, b).

Numerous women suffer from breast cancer every year and though this disease is lethal, there is a need for new therapeutic approaches which surpasses the shortcomings of the present treatments (Kumar et al. 2015). α-Lipoic acid inhibits cell proliferation via the epidermal growth factor receptor (EGFR) and the protein kinase B (PKB), also known as the Akt signaling, and induces apoptosis in human breast cancer cells (Na et al. 2009). α-Lipoic acid tramps the ROS followed by arrest in the G1 phase of the cell cycle and activates p27 (kip1)-dependent cell cycle arrest via changing of the ratio of the apoptotic-related protein Bax/Bcl-2 (Dozio et al. 2010). α-Lipoic acid drives pyruvate dehydrogenase by downregulating aerobic glycolysis and activation of apoptosis in breast cancer cells, lactate production, induces apoptosis, and diminishes cell viability, implying that the inadequate uptake might be due to reduced cell death caused by α-lipoic acid (Feuerecker et al. 2012).

Most basic symptoms of colon cancer are rectal bleeding and anemia. These symptoms sum up and lead to changes in bowel habits and weight loss, with a complication of uncontrolled cell growth in the colon, leading to colorectal cancer which is the third most diagnosed cancer in the

world (Malgras et al. 2016). Dihydrolipoic acid scavenges the cytosolic oxygen in HT-29 human colon cancer cells; furthermore, it escalates in a dose-dependent manner the caspase-3-like activity associated with DNA fragmentation. It was concluded that α-lipoic acid induces apoptosis by a pro-oxidant mechanism triggered by an escalated uptake of mitochondrial substrates in oxidizable form (Wenzel et al. 2005). This involves monocarboxylates uptake amplification in mitochondria through glycolysis after their oxidation into the citric acid cycle, and then the increased depletion equivalents delivery into the respiratory chain drastically increases the production of mitochondrial oxygen. This high oxygen burden overcomes the high antioxidative capacity of anti-apoptotic proteins and allows apoptosis to be executed in tumor cells (Kang et al. 2015).

Metabolic Disease and Obesity

Lifestyle modification in daily activity and diet pattern is the foundation of an effective strategy to improve metabolic disorders and reduce obesity. α-Lipoic acid shows a wide array of metabolic benefits, including glucose lowering, anti-obesity, lipid lowering, and an insulin sensitizing effect (Carrier and Rideout 2013). α-Lipoic acid and coenzyme Q10 prevent apoptosis and degeneration of dorsal root ganglion (DRG) neurons mediated by regulation of uncoupling protein 2 (UCP2) and caspase-3 expression, inducing ATP and improving diabetic neuropathy induced changes in DRG neurons (Galeshkalami et al. 2018). It is used in the treatment of diabetic polyneuropathy and insulin resistance (Bustamante et al. 1998). According to a clinical study, α-lipoic acid supplementation reduces body weight and body mass index (Namazi et al. 2017). The combination of curcumin and α-lipoic acid reduces weight gain and adiposity. α-Lipoic acid helps in regenerating glutathione, along with vitamins C and E, and promotes glutathione synthesis. Hirata disease, or insulin autoimmune syndrome (IAS), is characterized by elevated insulin levels and anti-insulin autoantibodies. This disease is a rare form of autoimmune hypoglycemia caused by sulfhydryl-containing medicines, which trigger the creation of insulin autoantibodies. α-Lipoic acid has lately emerged as a cause of IAS. Furthermore, greater care is needed for suggesting this damage as a consequence of α-lipoic acid supplementation (Moffa et al. 2019).

Neuroprotective Effect

Free radical induced damaged makes an important contribution to secondary neuronal brain injury in stroke therapy (Dwivedi 2019). There is currently no treatment available to prevent this effect. The antioxidant property of α-lipoic acid is associated with its neurorestorative and neuroprotective effects. α-Lipoic acid administration (20 mg/kg) through jugular vein provides the neuroprotection by reducing the mortality, neurological deficit score, infarction, and increase neurogenesis and brain cell metabolism (Choi et al. 2013). α-Lipoic acid induces the M2 phenotype in microglia, modulates the expression of pro-inflammatory cytokines IL-6, IL-1, IL-10, and tumor necrosis factor (TNF), and inhibits the transcription factor NF-κB, a key mediator of inflammatory responses (Wang et al. 2018). Sleep is involved in regulating heat, maintaining energy, and recovering tissues. The protective effect of α-lipoic acid on social interaction memory was observed in sleep-deprived rats (Rezaie et al. 2020).

Neurodegeneration

In Parkinson's disease the MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), a neurotoxin that causes dopaminergic cell loss in mice model (Langston 1985). This neurotoxin triggers the death signaling pathway by activating apoptosis signal regulating kinase 1 (ASK1) and translocating the death domain associated protein (DAXX) in the substantia nigra pars compacta (SNpc) of mice; α-lipoic acid terminates this cascade and affords neuroprotection (Karunakaran et al. 2007). While oxidative stress is responsible for the degeneration of dopaminergic neurons in Parkinson's disease, α-lipoic acid mediates p53 protein repression and thereby escalates the expression levels of proliferating cell nuclear antigen (Li et al. 2016). Several studies have found that combining α-lipoic acid and omega-3 fatty acids has a synergistic effect in slowing functional and cognitive decline in Alzheimer's disease (Shinto et al. 2014). In scopolamine-induced memory loss, α-lipoic acid inhibits brain weight loss, downregulates oxidative tissue damage resulting in neuronal cell loss, repairs memory and motor function, reduces reactive astrocyte proliferation, and decreases chromatolysis in the cerebello-hippocampal cortex (Bastianetto and Quirion 2004). α-Lipoic acid also finds usefulness in other neurodegenerating diseases like Huntington's disease, ataxia telangiectasia (Andreassen et al. 2001).

Cardiovascular Disease

Oxidative alteration of low-density lipoprotein enhances atherogenicity (Wollin and Jones 2003). It has been discovered that macrophages, smooth muscle cells, and ROS scavenger receptors on monocytes unrestrainedly take oxidized LDL, resulting in lipid accumulation and the formation of atherosclerotic plaques. Enhanced oxidative stresses as well as inflammatory action give rise to hydroxyl radicals, peroxides, and superoxides inside the endothelium, which accelerate the progression of cardiovascular disease. The inflammatory conditions continue to harm the vasculature one after another (Wollin and Jones 2003). Dihydrolipoic

acid is reported for its blood lipid modulating characteristics, protection against LDL oxidation, and modulation of hypertension, indicating that α-lipoic acid might be a possible protective agent against cardiovascular diseases (Wollin and Jones 2003). The incidence of cardiovascular diseases decreases as the dietary intake of α-lipoic acid increases.

Kidney-Related Disease

Chronic kidney disease is a gradual loss of kidney function that leads to the accumulation of waste products in the blood. Diabetes and high blood pressure are two of the major risk factors for chronic kidney disease (Granata et al. 2015). In this condition, cellular metabolic changes occur that may lead to the major production of free radicals that play a crucial role in the development of renal damage and the onset of treatment resistance. Hypoxia, ROS, and oxidative stress may cause severe kidney injury and ischemic reperfusion injury (Zhang and McCullough 2016). Patients suffering from end-stage renal disease and kept on hemodialysis have very high chances of cardiovascular mortality (Levey et al. 1998). Intravenous iron infusion has become an essential segment of anemia management in end-stage renal disease patients. Iron injection intake leads to oxidative stress in the patients (Lim et al. 1999). After administration of intravenous iron, oxidative stress markers formed, including lipid hydroperoxide, F2 isoprostane, and malondialdehyde, a reactive aldehyde that gives rise to toxic stress in cells (Del et al. 2005). Research shows that after the administration of intravenous iron to chronic kidney disease and hemodialysis patients, malondialdehyde increases speedily (Lim et al. 1999; Agarwal et al. 2004). The generation of lipid hydroperoxide results in oxidative damage in lipoproteins, cell membranes, and other lipid-containing structures (Girotti and Kriska 2004). Administration of α-lipoic acid (600 mg/day) with antioxidants such as α-tocopherol or vitaminin E (300–1000 mg/day), and *N*-acetylcysteine (600–1200 mg/day) can help dialysis patients with elevated oxidative stress (Lim et al. 1999; Nazrul et al. 2000; Roob et al. 2000; Leehey et al. 2005). The antioxidant activities of α-lipoic acid were better than *N*-acetylcysteine at curing oxidative stress, including diabetic neuropathy and glomerular injury. α-Lipoic acid administration leads to a reduction in oxidative stress markers (low-density lipoprotein oxidizability and plasma protein carbonyls); thus, it is appreciable that administration of this agent may reduce oxidative stress induced by intravenous IV iron (Marangon et al. 1999). However, in diabetic nephropathy, TGFβ1 is related to MAPK and induces the production of fibronectin in mesangial cells. α-Lipoic acid ameliorates the proteinuria by decreasing expressions of the TGFβ1 and fibronectin protein (Lee et al. 2009). The patients with autosomal dominant polycystic kidney disease treated with α-lipoic acid showed a significant improvement in metabolic, inflammatory, and endothelial functions (Lai et al. 2020).

Inflammatory Disease

As a short-chain fatty acid, α-lipoic acid is synthesized inside the human body to work as an antioxidant, safeguarding body cells from injury, and helping restore the scales of other antioxidants, like vitamins C and E (Moura et al. 2021). Several studies have shown that combining α-lipoic acid with fructose can reduce fructose-induced inflammation, hepatic oxidative stress, and insulin resistance. It is also found that α-lipoic acid can act as a chemopreventive agent because it inhibits the inflammation linked to carcinogenesis (Moon 2016). α-Lipoic acid can reduce inflammatory markers in patients with heart disease, as oxidative stress is assumed to be the main cause of many cardiovascular diseases, together with hypertension, and heart failure. Oxidative stress increases during the aging process, resulting in either enhanced ROS generation or diminished antioxidant safeguards. The incidence of cardiac disease is directly related to one's age. Aging is also related to oxidative stress, which in turn leads to hastened cellular senescence and organ dysfunction. Antioxidants may assist in reducing the incidence of some pathologies of heart diseases and have anti-aging properties (Wollin and Jones 2003). Several studies also show that infusion of irbesartan and α-lipoic acid to patients with the metabolic syndrome diminishes proinflammatory markers and enhances endothelial function, elements that are indicated in the pathogenesis of atherosclerosis (Sola et al. 2005). Along with that, it is found that α-lipoic acid can protect the liver from inflammatory disorders as well. Additionally, α-lipoic acid may help reduce the blood levels of several inflammatory markers, including IL-6 and ICAM-1 (Liu et al. 2015). The recommended dosage for α-lipoic acid was found to be 300–600 mg daily and no problems have been found in people having 600 mg/day for up to 7 months (Liu et al. 2015).

Infertility

Infertility is defined as the inability to conceive after engaging in regular sexual activity without using contraception for at least a year. Infertility affects more than 15% of married couples worldwide, with men making up around 50% of those who are infertile (Jungwirth et al. 2012). Numerous medications have been utilized to improve sperm quality due to therapeutic limitations (Dong et al. 2019). Male infertility is partially caused by anatomical anomalies such as ductal blockages, varicocele, and ejaculatory problems. According to estimates, reduced sperm production of unknown origin is to blame for 40 to 90% of cases (Balercia et al. 2005). Depending on the kind and concentration of

the ROS as well as the location and length of exposure to the ROS, sperm function may be positively or negatively impacted by ROS (Thuwanut et al. 2010). According to studies, male germ cells can create ROS at different stages of their development. Leukocytes' excessive generation of ROS in semen and defective spermatozoa may contribute to infertility (Gharagozloo and Aitken 2011). Due to the depletion of intracellular ATP and the reduced phosphorylation of axonemal proteins, it has been discovered that somewhat elevated quantities of ROS have no effect on sperm survival but instead render them immobile (Takei et al. 2012). Excessive hydrogen peroxide concentrations, a major ROS producer, also cause lipid peroxidation and cell death. By reducing ROS generation, antioxidant medications maintain sperm viability and motility and can help safeguard sperm DNA integrity. Consuming dietary antioxidants may also improve semen conditions. It has been determined that male infertility is associated with a lower intake of specific antioxidant nutrients, such as vitamins A, C, and E, folate, zinc, carnitine, and selenium (Buhling and Laakmann 2014). α-Lipoic acid is also a powerful antioxidant that helps in the regulation of ROS production. α-Lipoic acid or its reduced form (dihydrolipoic acid) quenches several oxygen-free radical species in both aqueous and lipid phases (Sacks et al. 2018). The available report suggests that α-lipoic acid could improve the sperm motility rate and reduce sperm DNA damage, thereby improving sperm quality (Ibrahim et al. 2008). Also, α-lipoic acid shows the positive effect in oocyte maturation, embryo development, and reproductive outcome (Dong et al. 2019; di Tucci et al. 2021). Regular administration of α-lipoic acid reduces the pelvic pain in endometriosis and regularizes the menstrual blood flow. α-Lipoic acid represents a promising new molecule for infertility and additional clinical studies are recommended in the future. Cigarette smoking is a detrimental effect on the genital system of rat models due to oxidative stress. Smoking has a negative effect on the genital system via hypoxia-inducible factors (HIF-1α and HIF-2α), TNF-α, caspase 3, and the calcitonin gene-related peptide (CGRP) in the uterus, and α-lipoic acid protected against the negative effects on the female reproductive system (Asci et al. 2018). α-Lipoic acid also promoted decreasing effects of nicotine-induced skin, lung, and liver damage (Ateyya et al. 2017; Yıldırım Baş et al. 2017).

Antimicrobial Activity

Microorganisms are responsible for various types of skin- and gut-related disorders. The gradual enhancements in the rapidity of resistance to antibiotics turn to rise in oral pathologies. α-Lipoic acid was found to inhibit the growth of various oral microorganisms to a large extent, such as *Pseudomonas* species, *Escherichia coli*, *Staphylococcus aureus*, and *Candida albicans*. α-Lipoic acid can arrest the growth of *Candida albicans* thereby exhibiting antifungal activity which is directly proportional to its concentration (Zhao et al. 2018). α-Lipoic acid also arrests the growth of *Cronobacter sakazakii* strains with the minimum inhibitory concentration (MIC) in the range from 2.5 to 5 mg/ml. It was corroborated that α-lipoic acid shows antimicrobial potential for affecting the membrane integrity, causing dysfunction of the cell membrane and alterations in cellular morphology. Recent studies also state that ALA is also effective against *Rickettsia rickettsii*, which is a constrained intracellular bacterium that generates Rocky Mountain spotted fever. α-Lipoic acid has significant ability to penetrate nucleus and affect intracellular actin-based mobility (Eremeeva and Silverman 1998; Sahni et al. 2019). α-Lipoic acid has the potential for protection against mycotoxin and treatment of mycotoxicosis (Rogers 2003). Another report suggested that α-lipoic acid has protective efficacies against aflatoxin B1-induced oxidative damage in the liver (Li et al. 2014). The beneficial effect of α-lipoic acid combined with other antioxidants, such as epigallocatechin gallate, affects the life span and age-dependent behavior of the nematode *Caenorhabditis elegans* (Phulara et al. 2021). In a nutshell, α-lipoic acid is an important molecule as antimicrobial, antifungal, antinematodal, and antiviral properties affecting multiple targets.

Polycystic Ovarian Syndrome

α-Lipoic acid (400 mg/day) in combination with myo-inositol (1 mg/day) against polycystic ovary syndrome (PCOS) improved hormonal and metabolic aspects and the insulin response to oral glucose tolerance test showed promising results in 90 obese patients (Genazzani et al. 2019). This combination affects the menstrual rate of women with PCOS positively, irrespective of their metabolic phenotype and with a higher dose of myo-inositol more evident and insulin-independent effect is seen (de Cicco et al. 2017; Fruzzetti et al. 2020). Integrative administration of α-lipoic acid (400 mg/day) improves the metabolic impairment in all PCOS patients with those who have a high risk of non-alcoholic fatty liver disease and predisposition to diabetes (Genazzani et al. 2018). D-Chiro-inositol and α-lipoic acid, in a combination treatment, may have a strong impact on metabolic profile in women with PCOS (Cianci et al. 2015; Fruzzetti et al. 2019). In PCOS, α-lipoic acid also decreases oxidative damage and insulin resistance. Endometriosis can be prevented and treated by a combination of *N*-acetyl cysteine, α-lipoic acid, and bromelain. α-Lipoic acid supplementation in patients with a suspected miscarriage to improve subchorionic hematoma resorption is a promising field of investigation. In addition, α-lipoic acid could be used to prevent diabetic embryopathy and premature fetal

membrane rupture caused by inflammation. Finally, α-lipoic acid can be used safely to treat neuropathic pain and as a dietary supplement during pregnancy (di Tucci et al. 2018).

COVID-19

The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) epidemic COVID-19 has emerged as a rapidly spreading communicable disease that currently affects all nations throughout the world. Although the virus has been found in the stool and urine of infected people, the likelihood of alternative channels of transference cannot be ruled out. The sickness is primarily spread through large respiratory droplets (Princess 2020). Diabetes patients are more likely to get an infection. According to research, patients with the coronavirus that causes the severe acute respiratory syndrome (SARS) and pandemic influenza A 2009 were seen as having diabetes as a substantial risk factor for mortality with H1N1 influenza (Yang et al. 2006; Schoen et al. 2019; Song et al. 2019). Of people who died from COVID-19 in Wuhan, China, 42.3% had diabetes. According to a theory (Sayıner and Serakıncı, 2021), α-lipoic acid controls the immune system by controlling T-cell activation, making it a useful treatment candidate for the cytokine storm that causes SARS-CoV-2 infection. According to studies, treating diabetic patients with α-lipoic acid will help them fight COVID-19 (Cure and Cure 2020). The human host is protected against SARS-CoV-2 by α-lipoic acid via opening ATP-dependent K^+ channels (Na^+, K^+-ATPase), which in turn increases intracellular pH and inhibits virus entry.

Effects on Gut Microbiota

α-Lipoic acid is a short-chain fatty acids (SCFAs) derived from the fermentation of vegetables and meat and modulates the gut microbiota without reducing the microbial diversity (Tripathi et al. 2022; Yadav et al. 2022a, b). A recent study showed that α-lipoic acid and the SCFAs produced by *Ruminococcaceae* rejuvenated aged intestinal stem cells by preventing the age-associated endosome reduction (Du et al. 2020; Xiong et al. 2022). α-Lipoic acid takes part in crucial biological operations, together with the fixation and modulation of mitochondrial multi-enzyme complexes, oxidation of amino acids and carbohydrates, removal of ROS, and harmonization of energetic metabolism (Shay et al. 2009; Schultz and Sinclair 2016). At a younger age, the human body can synthesize α-lipoic acid itself in the required amount, but its quantity remarkably decreases with age, which is supposed to be connected to age-related organic dysfunction (Hagen et al. 2002; Park et al. 2021), so to reduce age-related disorders, α-lipoic acid is used as a natural supplement. *Drosophila* midgut is an appropriate prototype structure for the learning of mechanisms underlying the age-associated decline in stem cell function. A decrease in differentiation efficiency and a malignant increase in proliferation rate takes place in the intestinal stem cells inside the midguts of *Drosophila* when it ages. This leads the way to the sustained accumulation of escargot embryonal stem gene (Esg +) cells in intestinal stem cells and their differentiating progenies in the midguts of aged flies (Choi et al. 2008; Hochmuth and Jasper 2008; Cui et al. 2019). Liquid chromatography-electrospray ionization-mass spectrometry (LC–ESI–MS/MS) analyses were carried out which illustrated the profusion of α-lipoic acid decline in guts of aged flies. Thus, the mRNA and protein expression of Las in *Drosophila* intestinal stem cells go through a significant depletion in response to aging, which in turn causes a curtailment of α-lipoic acid in midguts of aged flies. α-Lipoic acid insertion sets up at an intermediate age (26–27 days) and showed a most remarkable repressive outcome of Esg + cell accumulation in aged (40 days) *Drosophila* midgets (Park et al. 2021).

Molecular Targets

α-Lipoic acid has so many molecular targets for disease management and biological action (Fig. 3), among them significant ones are voltage-gated potassium channels, epoxide hydrolase, and leukotriene A4 hydrolase (Maldonado-rojas et al. 2011). It doubles the levels of PPAR-mRNA and protein while decreasing the activation of the c-Jun *N*-terminal kinase (JNK) signaling pathway (Rousseau et al. 2016), a member of the MAPK (mitogen-activated protein kinase) family that regulates a range of biological processes implicated in tumorigenesis and neurodegenerative disorders. α-Lipoic acid reduces endoplasmic reticulum stress and enhances glucose absorption by targeting the DNAJB3 (DnaJ heat shock protein family) and mRNA molecule (Diane et al. 2020). According to reports, it lowers the NALP-3 inflammasome in the endometrium of women who experience idiopathic recurrent pregnancy loss (Di et al. 2019). By inhibiting breast cancer cell proliferation, cell cycle progression, and the epithelial-to-mesenchymal transition, α-lipoic acid has significant antiproliferative effects. By blocking the transforming growth factor beta (TGFβ) signaling pathway, α-lipoic acid prevents breast cancer cells from migrating and encroaching (Tripathy et al. 2018). However, α-lipoic acid blocks the cAMP-response element binding protein (CREB)/furin axis in breast cancer cell lines to prevent furin production in estrogen receptor (+) and (−) breast cancer cell lines (Farhat et al. 2020). Glucose fluctuations in diabetic encephalopathy encourage neuronal death. α-Lipoic acid has renoprotective effects on rat kidneys damage brought on by iron overload through inhibiting NADPH oxidase 4 and p38 MAPK signaling (Cavdar et al. 2020). α-Lipoic acid also exhibited neuroprotective effects in response to the glucose fluctuation by increasing the expression of TrkA/p75NTR

and p-AKT/AKT pathways (Yan et al. 2020). α-Lipoic acid diminishes the serum immunoglobulin E (IgE) levels of the atopic dermatitis mice model and enhances splenic B cell counts in endotoxemia mice which showed that IgE plays a modulating role in the expansion, death, and function of B-cells. Recent studies show that α-lipoic acid enhances cAMP synthesis by activation of EP2 and EP4 prostaglandin receptors in peripheral blood T-cells. The enhanced level of cAMP inside cells reduces the expression of IL-2 and IL-2Rα (CD25) that in turn influence expansion, death, and function of T-cells. Natural killer (NK) cells have two main functions: cytotoxicity and interferon gamma (IFN-γ) secretion. IFN-γ is a powerful macrophage activator for both lysis and phagocytosis. α-Lipoic acid hampers IFN-γ secretion induced by IL-12/IL-18 and cellular cytotoxicity in NK cells which enhances cAMP production via G protein-coupled receptors (Liu et al. 2019).

Although α-lipoic acid has long been discovered as an antioxidant, it has also been demonstrated to improve glucose and ascorbate treatment, activate phase II detoxification via the transcription factor Nrf2, increase eNOS activity, and lower expression of MMP-9 and VCAM-1 through repression of NF-κB. α-Lipoic acid and its reduced form, dihydrolipoic acid, could be used for their chemical properties as a redox pair to modify protein conformations by forming mixed disulfides. Beneficial effects are accomplished with low micromolar levels of α-lipoic acid, suggesting that its therapeutic potential extents beyond the precise definition of an antioxidant agent.

Toxicological Effects

α-Lipoic acid is a well-known antioxidant consumed to remedy a variety of disorders, though it is assumed a very secure supplement and intoxication is extremely infrequent, acute excessive-dose ingestions can cause mortality (Emir et al. 2018). The safety of α-lipoic acid can be evaluated using sub-chronic and acute toxicity studies. α-Lipoic acid at the excessive dose of 121 mg/kg BW for 4 weeks to male/female Wistar rats corroborated little changes in liver enzymes; in addition, insignificant histopathological effects on the liver and mammary glands were observed (Cremer et al. 2006). Studies have estimated an adult dose of α-lipoic acid up to 2400 mg with no severe side effects; however, excessive dose of α-lipoic acid is not suggested as it does not add any other therapeutic or nutritional advantage (Cremer et al. 2006), whereas the daily oral supplementation of 600 mg of α-lipoic acid during pregnancy does not cause any side effects to both mothers and newborns; however, medical supervision is strictly suggested (Jibril et al. 2022). Furthermore, studies associated with α-lipoic acid conducted on primates displayed that more lethal dose would lead to hepatic necrosis, indicating that excess doses of intravenous α-lipoic acid can be able to produce resistance (Vigil et al. 2014). α-Lipoic acid has also been shown to reverse the adverse health effects of mycotoxins (Rogers 2003). Skin and gastrointestinal disorders are the most frequently reported adverse effects for α-lipoic acid-containing dietary supplements (Gatti et al. 2021). Allergic reactions like rashes, hives, and itching are the side effects of the oral intake of α-lipoic acid. However, effects like vertigo, diarrhea, and vomiting are dose dependent. It is suggested that the use of α-lipoic acid should be discouraged immediately if any allergic reaction occurs (Ziegler et al. 2016).

Nanoformulations

α-Lipoic acid is used either as an excipient or as a main therapeutic ingredient in various types of nanoformulations (size of about 1–1000 nm); due to this small size, it has a very large surface area and hence high area of contact which enhances the therapeutic effect of drug particle incorporated (Jong and Borm 2008). It can be formulated in the form of nanostructure lipid carriers, solid lipid nanoparticles, and nano-emulsion. Silver nanoparticles (AgNPs) are extensively considered for their broad-spectrum antimicrobial outcome and can be employed instantly in biomaterials; however, the cellular protection of specific AgNP formulations should be profiled earlier for clinical utilization. α-Lipoic acid is used as a capping agent that plays an important role because it can alter aggregation profiles, nanoparticles–cell interactions, and free Ag^+ ion release, all known variables that affect cytotoxicity (Beer et al. 2012). AgNPs can be able to outcome the evocation of oxidative harm and inflammatory lesions in human gingival fibroblast cells (Jin et al. 2012). AgNPs capped with α-lipoic acid decrease toxicity as compared to other capping agents (Verma et al. 2018). Studies show that α-lipoic acid-capped AgNPs possess antimicrobial effects at low concentrations (2.5–12.5 µg/ml). Docetaxel, acytotoxic taxane diterpenoid sold under the brand name taxotere, is an antimicrotubule agent effective as chemotherapy medication to treat several types of cancer, including metastatic breast cancer (Lyseng-Williamson and Fenton 2005). Co-delivery of docetaxel and α-lipoic acid using solid lipid nanoparticles (SLNs) as a carrier demonstrated remarkably higher uptake efficiency along with better cytotoxic and apoptotic capability and assured a better treatment of breast cancer (Kothari et al. 2019). The anti-inflammatory, antioxidant, and anti-apoptotic actions of α-lipoic acid, as well as the effectiveness of the encapsulation approach, can boost the efficiency and stability of α-lipoic acid, and reduce the neurotoxicity caused by AlCl3. Furthermore, α-lipoic acid-SLNs outperform α-lipoic acid-chitosan nanoparticles (Metwaly et al. 2022) (Fig. 5).

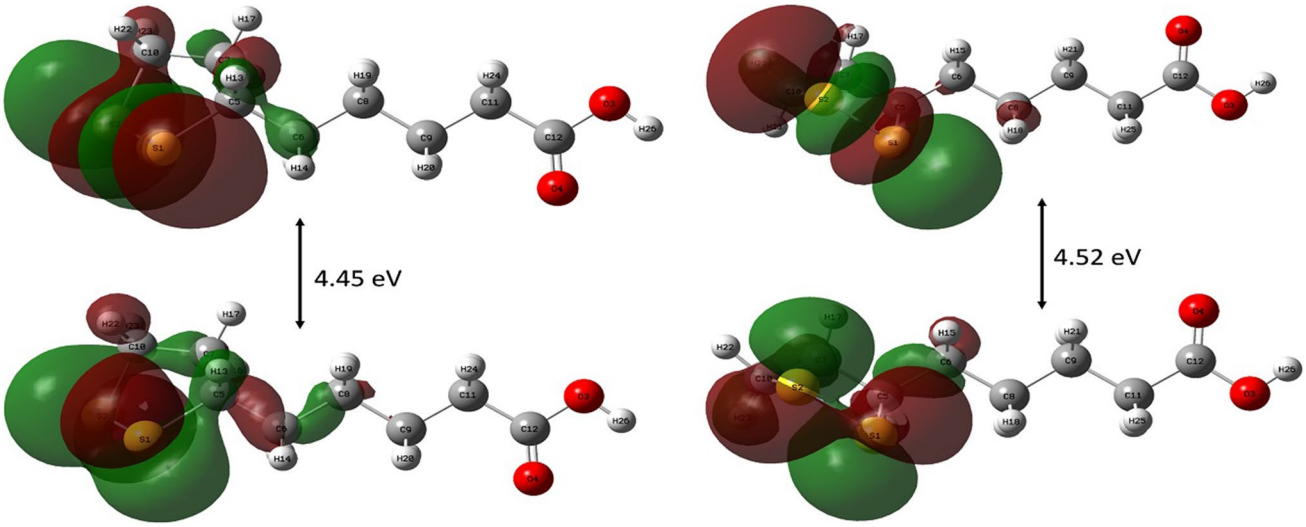


Fig. 5 HOMO–LUMO plots of the two enantiomers of α-lipoic acid **a** *S*-enantiomer; **b** *R*-enantiomer

Perspectives and Future Directions

The biological roles of α-lipoic acid are highly varied, as this review has shown. In fact, as a bioactive agent, we are aware of only a few substances that act as diverse as α-lipoic acid. Its therapeutical effects consist of a metallic chelator, a vasorelaxant/antihypertensive, an inductor of cell signaling pathways, an insulin mimic, a hypotriglycemic agent, a vasorelaxant, and an adjuvant for neurocognitive function. Determining the specific cause-and-effect relationship between α-lipoic acid and its cellular targets will therefore be crucial. Whether α-lipoic acid directly controls the hormonal signals that trigger subsequent pharmacological effects on target organs is a subject that needs more investigation. In this way, α-lipoic acid strengthens learning and short-term memory in aged rodents and encourages an anorectic effect in rodents that is AMPK-dependent (Shay et al. 2009). Only 12% of the dose that was delivered is recovered as the parent chemical in the urine. In contrast, results from animal experiments showed that more than 80% of the injected radioactive-labeled dose was recovered through urine. Given that α-lipoic acid is almost entirely absorbed from the human gastrointestinal tract, metabolized, and excreted, negligible free α-lipoic acid is retained in tissues. As recently established in mice, rats, and dogs, different β-oxidation and mono- and bis-*S*-methylation products of the sulfydryl groups appear to be implicated in urine metabolic patterns (Fig. 6). Additionally, biliary elimination should be the focus of future research on the human metabolism of α-lipoic acid (Teichert et al. 2003).

Conclusion

Many studies have reported on the pleiotropic and medicinal activities of α-lipoic acid since its discovery in 1937, followed by isolation and synthesis in the 1950s (Gomes and Negrato 2014). A molecular and electronic structure study of α-lipoic acid suggests that its antioxidant potential is responsible for its anti-disease activities. However, preclinical and clinical studies form the foundation of much of the discussion presented here. As a result, α-lipoic acid has powerful anti-disease properties, such as those against cancer, metabolic syndrome, and inflammatory diseases. Several potential molecular targets have been investigated in relation to a variety of diseases. The capacity of this substance to neutralize ROS, lessen oxidative stress, and trigger apoptosis is the fundamental mechanism underlying its effectiveness against various diseases and chronic disorders. Additional investigation is required into the various metabolic products generated by the gut microbiota following the microbial degradation of α-lipoic acid and its related analogs because these products, which were confirmed by LC–MS/MS chromatography, may be a significant factor in the toxicity of various organs. In all the clinical trials that were conducted with α-lipoic acid, it was either used alone or in conjunction with other medications. The safe dose for action was reported to be between 300 and 1800 mg per day for the term stated for each illness condition. In the context of COVID-19, it is also hypothesized as a repurposed drug to investigate the inhibitory action on new molecular targets. However, it is important to design computational studies and in vitro and in vivo investigations to offer comprehensive proof.

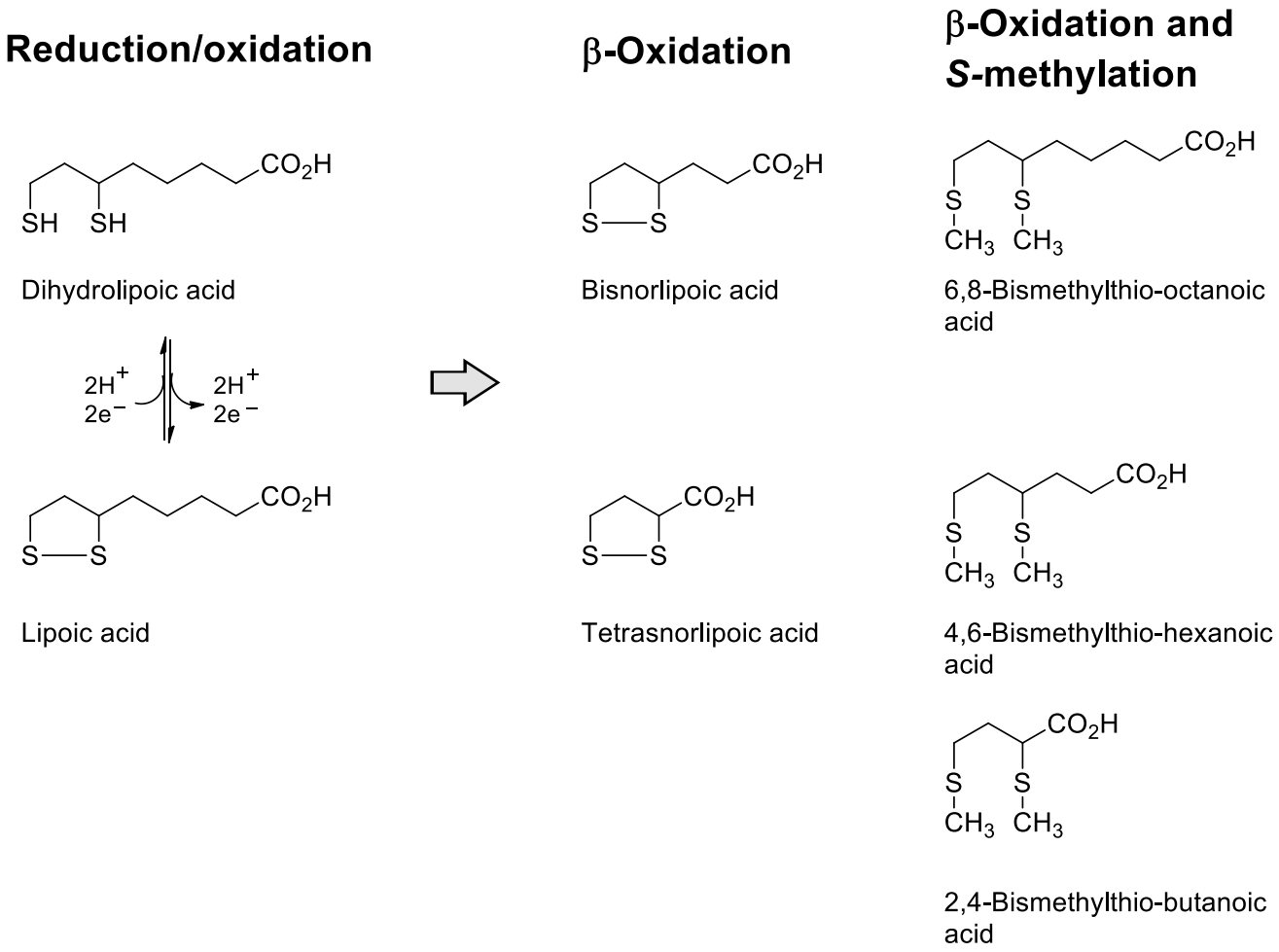


Fig. 6 Lipoic acid and its reduced form, dihydrolipoic acid, with the most common metabolites

Based on the information presented here, α-lipoic acid is useful in the treatment of reproductive diseases, which has been briefly explored in the context of polycystic ovary syndrome. With respect to neurodegenerative diseases, including Parkinson's disease, Alzheimer's disease, Huntington's disease, and telangiectasia ataxia, the neuroprotective activity of α-lipoic acid is discussed and demonstrated to be promising. Despite all these reports and multiple clinical trials, it has not yet been approved for use in humans. Although its bioavailability is increased in the form of nanoformulations, α-lipoic acid changes the metabolism and bioavailability of co-administered medicines when taken in combination. Despite there being few active clinical trials, this chemical is the subject of an increasing number of publications. As new information about the health benefits of α-lipoic acid will be gathered, its use in the clinic is more likely to be widely accepted.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s43450-023-00370-1.

Author Contribution AKT started the project by developing the titles and subtitles, has done extensive correction of the assigned title and subtitle in the manuscript, and revised the manuscript by careful consideration of the reviewer and editorial comments. AKR wrote full manuscript and implemented all correction guided by AKT, SKM, and HM; drew all figures diagram; and made Tables S1 and S2. SKM provided the facility and collaborative efforts for development of the manuscript, and provided extensive suggestions and explained the technical terms in the revised manuscript. SMB wrote and drew the electronic molecular structure for α-lipoic acid. HM guided the molecular electronic structure of the α-lipoic acid and performed the extensive correction for manuscript and implemented comments. AK performed initial research work and partially written assigned title and subtitle. All the authors have read the final manuscript and approved the submission.

References

Andreassen OA, Ferrante RJ, Dedeoglu A, Beal MF (2001) Lipoic acid improves survival in transgenic mouse models of Huntington's disease. NeuroReport 12:3371–3373. https://doi.org/10.1097/00001756-200110290-00044

Asci H, Erol O, Ellidag HY, Tola EN, Savran M, Ozmen O (2018) Pathology of cigarettes on the reproductive system and ameliorative effects of alpha lipoic acid: a rat model study. Toxicol Ind Health 34:385–395. https://doi.org/10.1177/0748233718755160

Ateyya H, Nader MA, Attia GM, El-Sherbeeny NA (2017) Influence of alpha-lipoic acid on nicotine-induced lung and liver damage in experimental rats. Can J Physiol Pharmacol 95:492–500. https://doi.org/10.1139/cjpp-2016-0366

Attia M, Essa EA, Zaki RM, Elkordy AA (2020) An overview of the antioxidant effects of ascorbic acid and alpha lipoic acid (in liposomal forms) as adjuvant in cancer treatment. Antioxidants 9:359. https://doi.org/10.3390/antiox9050359

Agarwal R, Vasavada N, Sachs NG, Shaw C (2004) Oxidative stress and renal injury with intravenous iron in patients with chronic kidney disease. Kidney Int 65:2279–2289. https://doi.org/10.1111/j.1523-1755.2004.00648.x.

Balercia G, Regoli F, Armeni T, Koverech A, Mantero F, Boscaro M (2005) Placebo-controlled double-blind randomized trial on the use of L-carnitine, L-acetylcarnitine, or combined L-carnitine and L-acetylcarnitine in men with idiopathic asthenozoospermia. Fertil Steril 84:662–671. https://doi.org/10.1016/j.fertnstert.2005.03.064

Bastianetto S, Quirion R (2004) Natural antioxidants and neurodegenerative diseases. Front Biosci Landmark 9:3447–3452. https://doi.org/10.2741/1493

Beer C, Foldbjerg R, Hayashi Y, Sutherland DS, Autrup H (2012) Toxicity of silver nanoparticles — nanoparticle or silver ion ? Toxicol Lett 208:286–292. https://doi.org/10.1016/j.toxlet.2011.11.002

Bingham PM, Stuart SD, Zachar Z (2014) Lipoic acid and lipoic acid analogs in cancer metabolism and chemotherapy. Expert Rev Clin Pharmacol 7:837–46. https://doi.org/10.1586/17512433.2014.966816

Bustamante J, Lodge JK, Marcocci L, Tritschler HJ, Packer L, Rihn BH (1998) α-Lipoic acid in liver metabolism and disease. Free Radical Biol Med 24:1023–1039. https://doi.org/10.1016/S0891-5849(97)00371-7

Brookes MH, Golding BT, Howes DA, Hudson AT (1983) Proof that the absolute configuration of natural α-lipoic acid is R by the synthesis of its enantiomer [(*S*)-(−)-α-lipoic acid] from (*S*)-malic acid. J Chem Soc Chem Comm 19:P1051-1053. https://doi.org/10.1039/C39830001051

Buhling KJ, Laakmann E (2014) The effect of micronutrient supplements on male fertility. Curr Opin Obstet Gyn 26:199–209. https://doi.org/10.1097/GCO.0000000000000063

Carrier B, Rideout TC (2013) Anti-obesity and lipid-lowering properties of alpha-lipoic acid. J Hum Nutr Food Sci 1:1008

Cavdar Z, Oktan MA, Ural C, Calisir M, Kocak A, Heybeli C, Yildiz S, Arici A, Ellidokuz H, Celik A, Yilmaz O (2020) Renoprotective effects of alpha lipoic acid on iron overload-induced kidney injury in rats by suppressing NADPH oxidase 4 and p38 MAPK signaling. Biol Trace Elem Res 193:483–493. https://doi.org/10.1007/s12011-019-01733-3

Choi HJ, Kim TY, Ruiz-Llorente S, Jeon MJ, Han JM, Kim WG, Shong YK, Kim WB (2012) Alpha-lipoic acid induces sodium iodide symporter expression in TPC-1 thyroid cancer cell line. Nucl Med Biol 39:1275–1280. https://doi.org/10.1016/j.nucmedbio.2012.08.007

Choi K, Kim J, Kim H (2013) α-Lipoic acid treatment is neurorestorative and promotes functional recovery after stroke in rats. J Neurol Sci 333:e195. https://doi.org/10.1016/j.jns.2013.07.784

Choi NH, Kim JG, Yang DJ, Kim YS, Yoo MA (2008) Age-related changes in *Drosophila midgut* are associated with PVF2, a PDGF/VEGF-like growth factor. Aging Cell 7:318–334. https://doi.org/10.1111/j.1474-9726.2008.00380.x

Cianci A, Panella M, Fichera M, Falduzzi C, Bartolo M, Caruso S (2015) D-chiro-inositol and alpha lipoic acid treatment of metabolic and menses disorders in women with PCOS. Gynecol Endocrinol 31:483–486. https://doi.org/10.3109/09513590.2015.1014784

Cremer DR, Rabeler R, Roberts A, Lynch B (2006) Safety evaluation of α-lipoic acid (ALA). Regul Toxicol Pharm 46:29–41. https://doi.org/10.1016/j.yrtph.2006.06.004

Cui H, Tang D, Garside GB, Zeng T, Wang Y, Tao Z, Zhang L, Tao S (2019) Wnt signaling mediates the aging-induced differentiation impairment of intestinal stem cells. Stem Cell Rev Rep 15:448–455. https://doi.org/10.1007/s12015-019-09880-9

Cure E, Cure MC (2020) Alpha-lipoic acid may protect patients with diabetes against COVID-19 infection. Med Hypotheses 143:110185. https://doi.org/10.1016/j.mehy.2020.110185

De Cicco S, Immediata V, Romualdi D, Policola C, Tropea A, Di Florio C, Tagliaferri V, Scarinci E, Della Casa S, Lanzone A, Apa R (2017) Myoinositol combined with alpha-lipoic acid may improve the clinical and endocrine features of polycystic ovary syndrome through an insulin-independent action. Gynecol Endocrinol 33:698–701. https://doi.org/10.1080/09513590.2017.1313972

Del Rio D, Stewart AJ, Pellegrini N (2005) A review of recent studies on malondialdehyde as toxic molecule and biological marker of oxidative stress. Nutr Metab Cardiovas 15:P316-328. https://doi.org/10.1016/j.numecd.2005.05.003

Di Nicuolo F, D'Ippolito S, Castellani R, Rossi ED, Masciullo V, Specchia M, Mariani M, Pontecorvi A, Scambia G, Di Simone N (2019) Effect of alpha-lipoic acid and myoinositol on endometrial inflammasome from recurrent pregnancy loss women. Am J Reprod Immunol 82:e13153. https://doi.org/10.1111/aji.13153

Di Tucci C, Di Feliciantonio M, Vena F, Capone C, Schiavi MC, Pietrangeli D, Muzii L, Benedetti Panici P (2018) Alpha lipoic acid in obstetrics and gynecology. Gynecol Endocrinol 34:729–733. https://doi.org/10.1080/09513590.2018.1462320

Di Tucci C, Galati G, Mattei G, Bonanni V, Capri O, D'Amelio R, Muzii L, Benedetti Panici P (2021) The role of alpha lipoic acid in female and male infertility: a systematic review. Gynecol Endocrinol 37:497–505. https://doi.org/10.1080/09513590.2020.1843619

Diane A, Mahmoud N, Bensmail I, Khattab N, Abunada HA, Dehbi M (2020) Alpha lipoic acid attenuates ER stress and improves glucose uptake through DNAJB3 cochaperone. Sci Rep 24:20482. https://doi.org/10.1038/s41598-020-77621-x

Dong L, Zhang X, Yang F, Li J, Yu X, Li Y (2019) Effect of oral alpha-lipoic acid (ALA) on the treatment of male infertility: a protocol for systematic review and meta-analysis. Medicine 98:e18453. https://doi.org/10.1097/MD.0000000000018453

Dozio E, Ruscica M, Passafaro L, Dogliotti G, Steffani L, Pagani A, Demartini G, Esposti D, Fraschini F, Magni P (2010) The natural antioxidant alpha-lipoic acid induces p27Kip1-dependent cell cycle arrest and apoptosis in MCF-7 human breast cancer cells. Eur J Pharmacol 641:29–34. https://doi.org/10.1016/j.ejphar.2010.05.009

Du G, Qiao Y, Zhuo Z, Zhou J, Li X, Liu Z, Li Y, Chen H (2020) Lipoic acid rejuvenates aged intestinal stem cells by preventing age-associated endosome reduction. EMBO Rep 21:49583. https://doi.org/10.15252/embr.201949583

De Jong WH, Borm PJ (2008) Drug delivery and nanoparticles: applications and hazards. Int J Nanomed 3:133–149. https://doi.org/10.2147/ijn.s596

Del Rio C, Malani PN (2020) COVID-19—new insights on a rapidly changing epidemic. JAMA 323:1339–1340. https://doi.org/10.1001/jama.2020.3072

Dohle G, Jungwirth A, Colpi G, Giwercman A, Diemer T (2012) European Association of Urology Guidelines on Male Infertility: the 2012 update. Eur Urol 62:324–332. https://doi.org/10.1016/j.eururo.2012.04.048

Emir DF, Ozturan IU, Yilmaz S (2018) Alpha lipoic acid intoxicatıon: an adult. Am J Emerg Med 36:1125-e3. https://doi.org/10.1016/j.ajem.2018.03.022

Eremeeva ME, Silverman DJ (1998) Effects of the antioxidant α-lipoic acid on human umbilical vein endothelial cells infected with *Rickettsia rickettsii*. Infect Immun 66:2290–2299. https://doi.org/10.1128/IAI.66.5.2290-2299.1998

Freelan RO (1951) The green pigment and physiology of guard cells. Science 114:94–95. https://doi.org/10.1126/science.114.2952.94

Fruzzetti F, Benelli E, Fidecicchi T, Tonacchera M (2020) Clinical and metabolic effects of alpha-lipoic acid associated with two fifferent doses of myo-inositol in women with polycystic ovary syndrome. Int J Endocrinol 2020:2901393. https://doi.org/10.1155/2020/2901393

Fruzzetti F, Capozzi A, Canu A, Lello S (2019) Treatment with D-chiro-inositol and alpha lipoic acid in the management of polycystic ovary syndrome. Gynecol Endocrinol 35:506–510. https://doi.org/10.1080/09513590.2018.1540573

Galeshkalami NS, Abdollahi M, Najafi R, Baeeri M, Jamshidzade A, Falak R, Gholami MD, Hassanzadeh G, Mokhtari T, Hassani S, Rahimifard M (2018) Alpha-lipoic acid and coenzyme Q10 combination ameliorates experimental diabetic neuropathy by modulating oxidative stress and apoptosis. Life Sci 216:101–110. https://doi.org/10.1016/j.lfs.2018.10.055

Genazzani AD, Prati A, Marchini F, Petrillo T, Napolitano A, Simoncini T (2019) Differential insulin response to oral glucose tolerance test (OGTT) in overweight/obese polycystic ovary syndrome patients undergoing to myo-inositol (MYO), alpha lipoic acid (ALA), or combination of both. Gynecol Endocrinol 35:1088–1093. https://doi.org/10.1080/09513590.2019.1640200

Genazzani AD, Shefer K, Della Casa D, Prati A, Napolitano A, Manzo A, Despini G, Simoncini T (2018) Modulatory effects of alpha-lipoic acid (ALA) administration on insulin sensitivity in obese PCOS patients. J Endocrinol Invest 41:583–590. https://doi.org/10.1007/s40618-017-0782-z

Gharagozloo P, Aitken RJ (2011) The role of sperm oxidative stress in male infertility and the significance of oral antioxidant therapy. Hum Reprod 26:1628–1640. https://doi.org/10.1093/humrep/der132

Ghibu S, Richard C, Vergely C, Zeller M, Cottin Y, Rochette L (2009) Antioxidant properties of an endogenous thiol: alpha-lipoic acid, useful in the prevention of cardiovascular diseases. J Cardiovasc Pharmacol 54:391–398. https://doi.org/10.1097/FJC.0b013e3181be7554

Girotti AW, Kriska T (2004) Role of lipid hydroperoxides in photo-oxidative stress signaling. Antioxid Redox Signal 6:301–310. https://doi.org/10.1089/152308604322899369

Golbidi S, Badran M, Laher I (2011) Diabetes and alpha lipoic acid. Front Pharmacol 2:69. https://doi.org/10.3389/fphar.2011.00069

Gomes MB, Negrato CA (2014) Alpha-lipoic acid as a pleiotropic compound with potential therapeutic use in diabetes and other chronic diseases. Diabetol Metab Syndr 6:80. https://doi.org/10.1186/1758-5996-6-80

Granata S, Dalla Gassa A, Tomei P, Lupo A, Zaza G (2015) Mitochondria: a new therapeutic target in chronic kidney disease. Nutr Metabolism 12:49. https://doi.org/10.1186/s12986-015-0044-z

Guo Z, Lucchetta E, Rafel N, Ohlstein B (2006) Maintenance of the adult *Drosophila* intestine: all roads lead to homeostasis. Curr Opin Genet Dev 40:81–86. https://doi.org/10.1016/j.gde.2016.06.009

Gupta D, Bhattacharjee A (2019) Detailed investigation of *N*-(4-n-pentyl-oxybenzylidene)-4′-n-hexylaniline liquid crystal molecule. J Mol Struct 15:66–77

Hagen TM, Liu J, Lykkesfeldt J, Wehr CM, Ingersoll RT, Vinarsky V, Bartholomew JC, Ames BN (2002) Feeding acetyl-L-carnitine and lipoic acid to old rats significantly improves metabolic function while decreasing oxidative stress. Proc Natl Acad Sci 99:1870–1875. https://doi.org/10.1073/pnas.261708898

Huang Y, Zhu Z, Sun M, Wang J, Guo R, Shen L, Wu W (2012) Lipoic acid inhibits cell proliferation of tumor cells *in vitro* and *in vivo*. Cancer Biol Ther 13:1425–1435. https://doi.org/10.4161/cbt.22003

Ibrahim SF, Osman K, Das S, Othman AM, Majid NA, Rahman MP (2008) A study of the antioxidant effect of alpha lipoic acids on sperm quality. Clinics 63:545–550. https://doi.org/10.1590/S1807-59322008000400022

Islam KN, O'Byrne D, Devaraj S, Palmer B, Grundy SM, Jialal I (2000) Alpha-tocopherol supplementation decreases the oxidative susceptibility of LDL in renal failure patients on dialysis therapy. Atherosclerosis 150:217–224. https://doi.org/10.1016/S0021-9150(99)00410-4

Isenmann E, Trittel L, Diel P (2020) The effects of alpha lipoic acid on muscle strength recovery after a single and a short-term chronic supplementation — a study in healthy well-trained individuals after intensive resistance and endurance training. J Int Soc Sports Nutr 17:61. https://doi.org/10.1186/s12970-020-00389-y

Jiang H, Patel PH, Kohlmaier A, Grenley MO, McEwen DG, Edgar BA (2008) Article JNK activity in somatic stem cells causes loss of tissue homeostasis in the aging *Drosophila* gut. Cell Stem Cell 3:442–455. https://doi.org/10.1016/j.stem.2008.07.024

Jibril AT, Jayedi A, Shab-Bidar S (2022) Efficacy and safety of oral alpha-lipoic acid supplementation for type 2 diabetes management: a systematic review and dose–response meta-analysis of randomized trials. Endocr Connect 11. https://doi.org/10.1530/EC-22-0322.

Jocelyn PC (1967) The standard redox potential of cysteine-cystine from the thiol-disulphide exchange reaction with glutathione and lipoic acid. Eur J Biochem 2:327–331. https://doi.org/10.1111/j.1432-1033.1967.tb00142.x

Kang SJ, Lee YJ, Lee EK, Kwak MK (2012) Silver nanoparticles-mediated G2/M cycle arrest of renal epithelial cells is associated with NRF2-GSH signaling. Toxicol Lett 211:334–341. https://doi.org/10.1016/j.toxlet.2012.04.016

Kang J, Chong SJ, Ooi VZ, Vali S, Kumar A, Kapoor S, Abbasi T, Hirpara JL, Loh T, Goh BC, Pervaiz S (2015) Overexpression of Bcl-2 induces STAT-3 activation via an increase in mitochondrial superoxide. Oncotarget 6:34191–34205. https://doi.org/10.18632/oncotarget.5763

Karunakaran S, Diwakar L, Saeed U, Agarwal V, Ramakrishnan S, Iyengar S, Ravindranath V (2007) Activation of apoptosis signal regulating kinase 1 (ASK1) and translocation of death-associated protein, Daxx, in substantia nigra pars compacta in a mouse model of Parkinson's disease: protection by α-lipoic acid. FASEB J 21:2226–2236. https://doi.org/10.1096/fj.06-7580com

Keith DJ, Butler JA, Bemer B, Dixon B, Johnson S, Garrard M, Sudakin DL, Christensen JM, Pereira C, Hagen TM (2012) Age and gender dependent bioavailability of R-and R, S-α-lipoic acid: a pilot study. Pharmacol Res 66:199–206. https://doi.org/10.1016/j.phrs.2012.05.002

Kothari IR, Mazumdar S, Sharma S, Italiya K, Mittal A, Chitkara D (2019) Docetaxel and alpha-lipoic acid co-loaded nanoparticles for cancer therapy. Ther Deliv 10:227–240. https://doi.org/10.4155/tde-2018-0074

Kumar P, Kadakol A, Krishna Shasthrula P, Arunrao Mundhe N, Sudhir Jamdade V, Barua C, C, Bhanudas Gaikwad A, (2015) Curcumin as an adjuvant to breast cancer treatment. Anticancer Agents Med Chem 15:647–656. https://doi.org/10.2174/1871520615666150101125918

Lai S, Petramala L, Muscaritoli M, Cianci R, Mazzaferro S, Mitterhofer AP, Pasquali M, D'Ambrosio V, Carta M, Ansuini M, Ramaccini C (2020) α-Lipoic acid in patients with autosomal dominant polycystic kidney disease. Nutrition 71:110594. https://doi.org/10.1016/j.nut.2019.110594

Langston JW (1985) Mechanism of MPTP toxicity: more answers, more questions. Trends Pharmacol Sci 6:375–378. https://doi.org/10.1016/0165-6147(85)90176-2

Lee SJ, Kang JG, Ryu OH, Kim CS, Ihm SH, Choi MG, Yoo HJ, Kim DS, Kim TW (2009) Effects of α-lipoic acid on transforming growth factor β1-p38 mitogen-activated protein kinase-fibronectin pathway in diabetic nephropathy. Metabolism 58:616–623. https://doi.org/10.1016/j.metabol.2008.12.006

Leehey DJ, Palubiak DJ, Chebrolu S, Agarwal R (2005) Sodium ferric gluconate causes oxidative stress but not acute renal injury in patients with chronic kidney disease: a pilot study. Nephrol Dial Transpl 20:35–140. https://doi.org/10.1093/ndt/gfh565

Levey AS, Beto JA, Coronado BE, Eknoyan G, Foley RN, Kasiske BL, Klag MJ, Mailloux LU, Manske CL, Meyer KB, Parfrey PS (1998) Controlling the epidemic of cardiovascular disease in chronic renal disease: what do we know? What do we need to learn? Where do we go from here? National Kidney Foundation Task Force on Cardiovascular Disease. Am J Kidney Dis 32:853–906. https://doi.org/10.1016/s0272-6386(98)70145-3

Li DW, Wang YD, Zhou SY, Sun WP (2016) α-Lipoic acid exerts neuroprotective effects on neuronal cells by upregulating the expression of PCNA via the P53 pathway in neurodegenerative conditions. Mol Med Rep 14:4360–4366. https://doi.org/10.3892/mmr.2016.5754

Li Y, Ma QG, Zhao LH, Guo YQ, Duan GX, Zhang JY, Ji C (2014) Protective efficacy of alpha-lipoic acid against aflatoxinB1-induced oxidative damage in the liver. Asian-Australas J Anim Sci 27:907–915. https://doi.org/10.5713/ajas.2013.13588

Lim PS, Wei YH, Yu YL, Kho B (1999) Enhanced oxidative stress in haemodialysis patients receiving intravenous iron therapy. Nephrol Dial Transpl 14:2680–2687. https://doi.org/10.1093/ndt/14.11.2680

Liu W, Shi LJ, Li SG (2019) The immunomodulatory effect of alpha-lipoic acid in autoimmune diseases. BioMed Res Int 2019:8086257. https://doi.org/10.1155/2019/8086257

Liu Z, Guo J, Sun H, Huang Y, Zhao R, Yang X (2015) Biochimie α-lipoic acid attenuates LPS-induced liver injury by improving mitochondrial function in association with GR mitochondrial DNA occupancy. Biochimie 116:52–60. https://doi.org/10.1016/j.biochi.2015.06.023

Lyseng-Williamson KA, Fenton C (2005) Docetaxel Drugs 65:2513–2531. https://doi.org/10.2165/00003495-200565170-00007

Maldonado-Rojas W, Olivero-Verbel J, Ortega-Zuñiga C (2011) Searching of protein targets for alpha lipoic acid. J Braz Chem Soc 22:2250–2259. https://doi.org/10.1590/S0103-50532011001200003

Malgras B, Berger A, Bazeries P, Aubé C, Boudiaf M, Soyer P (2016) Imaging of complications of colonic stents. In: Tonolini, M. (eds) Imaging complications of gastrointestinal and biliopancreatic endoscopy procedures. Springer, Cham. https://doi.org/10.1007/978-3-319-31211-8_14.

Marangon K, Devaraj S, Tirosh O, Packer L, Jialal I (1999) Comparison of the effect of α-lipoic acid and α-tocopherol supplementation on measures of oxidative stress. Free Radic Biol Med 27:1114–1121. https://doi.org/10.1016/S0891-5849(99)00155-0

Metwaly HH, Fathy SA, Abdel Moneim MM, Emam MA, Soliman AF, El-Naggar ME, Omara EA, El-Bana MA (2022) Chitosan and solid lipid nanoparticles enhance the efficiency of alpha-lipoic acid against experimental neurotoxicity. Toxicol Mech Methods 32:268–279. https://doi.org/10.1080/15376516.2021.1998275

Moffa S, Improta I, Rocchetti S, Mezza T, Giaccari A (2019) Potential cause-effect relationship between insulin autoimmune syndrome and alpha lipoic acid: two case reports. Nutrition 57:1–4. https://doi.org/10.1016/j.nut.2018.04.010

Moon H (2016) Chemopreventive effects of alpha lipoic acid on obesity-related cancers. Ann Nutr Metab 68:137–44. https://doi.org/10.1159/000443994

Moura FA, Andrade KQ, Santos JCF, Goulart MOF (2021) Lipoic acid: its antioxidant and anti-inflammatory role and clinical applications 15:458-483. https://doi.org/10.2174/1568026615666150114161358

Na MH, Seo EY, Kim WK (2009) Effects of α-lipoic acid on cell proliferation and apoptosis in MDA-MB-231 human breast cells. Nutr Res Pract 3:265–271. https://doi.org/10.4162/nrp.2009.3.4.265

Namazi N, Larijani B, Azadbakht L (2017) Alpha-lipoic acid supplement in obesity treatment: a systematic review and meta-analysis of clinical trials. Clin Nutr 37:419–428. https://doi.org/10.1016/j.clnu.2017.06.002

Omran OM, Omer OH (2015) The effects of alpha-lipoic acid on breast of female albino rats exposed to malathion: histopathological and immunohistochemical study. Pathol Res Pract 211:462–469. https://doi.org/10.1016/j.prp.2015.02.006

Ou P, Tritschler HJ, Wolff SP (1995) Thioctic (lipoic) acid: a therapeutic metal-chelating antioxidant? Biochem Pharmacol 50:123–126. https://doi.org/10.1016/0006-2952(95)00116-H

Packer L, Witt EH, Tritschler HJ (1995) Alpha-lipoic acid as a biological antioxidant. Free Radical Biol Med 19:227–250. https://doi.org/10.1016/0891-5849(95)00017-R

Park S, Karunakaran U, Ho Jeoung N, Jeon JH, Lee IK (2014) Physiological effect and therapeutic application of alpha lipoic acid. Curr Med Chem 21:3636–45. https://doi.org/10.2174/0929867321666140706141806

Phulara SC, Pandey S, Jha A, Chauhan PS, Gupta P, Shukla V (2021) Hemiterpene compound, 3,3-dimethylallyl alcohol promotes longevity and neuroprotection in *Caenorhabditis elegans*. Geroscience 43:791–807. https://doi.org/10.1007/s11357-020-00241-w

Rezaie M, Nasehi M, Vaseghi S, Mohammadi-Mahdiabadi-Hasani MH, Zarrindast MR, Nasiri Khalili MA (2020) The protective effect of alpha lipoic acid (ALA) on social interaction memory, but not passive avoidance in sleep-deprived rats. N-S Arch Pharmacol 393:2081–2091. https://doi.org/10.1007/s00210-020-01916-z

Rogers SA (2003) Lipoic acid as a potential first agent for protection from mycotoxins and treatment of mycotoxicosis. Arch Environ Health 58:528–532. https://doi.org/10.3200/AEOH.58.8.528-532

Roob JM, Khoschsorur G, Tiran A, Horina JH, Holzer H, Winklhofer-Roob BM (2000) Vitamin E attenuates oxidative stress induced by intravenous iron in patients on hemodialysis. J Am Soc Nephrol 11:539–549. https://doi.org/10.1681/ASN.V113539

Rousseau AS, Sibille B, Murdaca J, Mothe-Satney I, Grimaldi PA, Neels JG (2016) A-lipoic acid up-regulates expression of peroxisome proliferator-activated receptor b in skeletal muscle: involvement of the JNK signaling pathway. FASEB J 30:1287–1299. https://doi.org/10.1096/fj.15-280453

Sacks D, Baxter B, Campbell BC, Carpenter JS, Cognard C, Dippel D, Eesa M, Fischer U, Hausegger K, Hirsch JA (2018) Multisociety consensus quality improvement revised consensus statement for endovascular therapy of acute ischemic stroke. Int J Stroke 13:612–632. https://doi.org/10.1177/1747493018778713

Sahni A, Fang R, Sahni SK, Walker DH (2019) Pathogenesis of Rickettsial diseases: pathogenic and immune mechanisms of an endotheliotropic infection. Annu Rev Pathol 14:127–152. https://doi.org/10.1146/annurev-pathmechdis-012418-012800

Salehi B, Berkay Yılmaz Y, Antika G, Boyunegmez Tumer T, Fawzi Mahomoodally M, Lobine D, Akram M, Riaz M, Capanoglu E, Sharopov F, Martins N (2019) Insights on the use of α-lipoic acid for therapeutic purposes. Biomolecules 9:356. https://doi.org/10.3390/biom9080356

Sayıner S, Serakıncı N (2021) Alpha-lipoic acid as a potential treatment for COVID-19 — a hypothesis. Curr Top Nutraceutical Res 19:172–175. https://doi.org/10.37290/ctnr2641-452x.19:172-175

Schoen K, Horvat N, Guerreiro NF, de Castro I, de Giassi KS (2019) Spectrum of clinical and radiographic findings in patients with diagnosis of H1N1 and correlation with clinical severity. BMC Infec Dis 19:964. https://doi.org/10.1186/s12879-019-4592-0

Schultz MB, Sinclair DA (2016) When stem cells grow old: phenotypes and mechanisms of stem cell aging. Development 143:3–14. https://doi.org/10.1242/dev.130633

Searls RL, Sanadi DR (1960) α-Ketoglutaric dehydrogenase: VIII. Isolation and some properties of a flavoprotein component. J Biol Chem 235:2485–2491. https://doi.org/10.1016/S0021-9258(18)64646-0

Shay KP, Moreau RF, Smith EJ, Smith AR, Hagen TM (2009) Alpha-lipoic acid as a dietary supplement: molecular mechanisms and therapeutic potential. BBA-General Subjects 1790:1149–1160. https://doi.org/10.1016/j.bbagen.2009.07.026

Sagi-Dain L, Sagi S, Dirnfeld M (2017) The effect of paternal age on oocyte donation outcomes. Obstet Gynecol Surv 71:301–306. https://doi.org/10.1097/01.pec.0000526609.89886.37

Shinto L, Quinn J, Montine T, Dodge HH, Woodward W, Baldauf-Wagner S, Waichunas D, Bumgarner L, Bourdette D, Silbert L, Kaye J (2014) A randomized placebo-controlled pilot trial of omega-3 fatty acids and alpha lipoic acid in Alzheimer's disease. J Alzheimer Dis 38:111–120. https://doi.org/10.3233/JAD-130722

Sola S, Mir MQ, Cheema FA, Khan-Merchant N, Menon RG, Parthasarathy S, Khan BV (2005) Irbesartan and lipoic acid improve endothelial function and reduce markers of inflammation in the metabolic syndrome: results of the Irbesartan and Lipoic Acid in Endothelial Dysfunction (ISLAND) study. Circulation 111:343–349. https://doi.org/10.1161/01.CIR.0000153272.48711.B9

Solmonson A, DeBerardinis RJ (2018) Lipoic acid metabolism and mitochondrial redox regulation. J Biol Chem 293:7522–7530. https://doi.org/10.1074/jbc.TM117.000259

Song Z, Xu Y, Bao L, Zhang L, Yu P, Qu Y, Zhu H, Zhao W, Han Y, Qin C (2019) From SARS to MERS, thrusting coronaviruses into the spotlight. Viruses 11:59. https://doi.org/10.3390/v11010059

Suh JH, Shenvi SV, Dixon BM, Liu H, Jaiswal AK, Liu RM, Hagen TM (2004) Decline in transcriptional activity of Nrf2 causes age-related loss of glutathione synthesis, which is reversible with lipoic acid. Proc Natl Acad Sci US A 101:3381–3386. https://doi.org/10.1073/pnas.0400282101

Takei GL, Mukai C, Okuno M (2012) Transient Ca 2 + mobilization caused by osmotic shock initiates salmonid fish sperm motility. J Exp Biol 15:630–641. https://doi.org/10.1242/jeb.063628

Teichret J, Hermann R, Ruus P, Preiss R (2003) Plasma kinetics, metabolism, and urinary excretion of alpha-lipoic acid following oral administration in healthy volunteers. J Clin Pharmacol 43:1257–1267. https://doi.org/10.1177/0091270003258654

Thuwanut P, Chatdarong K, Johannisson A, Bergqvist AS, Söderquist L, Axnér E (2010) Cryopreservation of epididymal cat spermatozoa: effects of *in vitro* antioxidative enzymes supplementation and lipid peroxidation induction. Theriogenology 73:1076–1087. https://doi.org/10.1016/j.theriogenology.2010.01.007

Tripathi AK, Ray AK, Mishra SK (2022) Molecular and pharmacological aspects of piperine as a potential molecule for disease prevention and management: evidence from clinical trials. Beni-Suef Univ J Basic Appl Sci 11:16. https://doi.org/10.1186/s43088-022-00196-1

Tripathy J, Tripathy A, Thangaraju M, Suar M, Elangovan S (2018) α-Lipoic acid inhibits the migration and invasion of breast cancer cells through inhibition of TGFβ signaling. Life Sci 207:15–22. https://doi.org/10.1016/j.lfs.2018.05.039

Trivedi P, Jena GB (2013) Role of α-lipoic acid in dextran sulfate sodium-induced ulcerative colitis in mice: studies on inflammation, oxidative stress, DNA damage and fibrosis. Food Chem Toxicol 59:339–355. https://doi.org/10.1016/j.fct.2013.06.019

Verma SK, Jha E, Panda PK, Mishra A, Thirumurugan A, Das B, Parashar SK, Suar M (2018) Rapid novel facile biosynthesized silver nanoparticles from bacterial release induce biogenicity and concentration dependent *in vivo* cytotoxicity with embryonic zebrafish—a mechanistic insight. Toxicol Sci 161:125–138. https://doi.org/10.1093/toxsci/kfx204

Vigil M, Berkson BM, Garcia AP (2014) Adverse effects of high doses of intravenous alpha lipoic acid on liver mitochondria. Glob Adv Health Med 3:25–27. https://doi.org/10.7453/gahmj.2013.011

Wang Q, Lv C, Sun Y, Han X, Wang S, Mao Z, Xin Y, Zhang B (2018) The role of alpha-lipoic acid in the pathomechanism of acute ischemic stroke. Cell Physiol Biochem 48:42–53. https://doi.org/10.1159/000491661

Wenzel U, Nickel A, Daniel H (2005) α-Lipoic acid induces apoptosis in human colon cancer cells by increasing mitochondrial respiration with a concomitant O2−.-generation. Apoptosis 10:359–368. https://doi.org/10.1007/s10495-005-0810-x

Wollin SD, Jones PJ (2003) α-Lipoic acid and cardiovascular disease. J Nutr 133:3327–3330. https://doi.org/10.1093/jn/133.11.3327

Xiong Y, Li Q, Ding Z, Zheng J, Zhou D, Wei S, Han X, Cheng X, Li X, Xue Y (2022) Dietary α-lipoic acid requirement and its effects on antioxidant status, carbohydrate metabolism, and intestinal microflora in Oriental River prawn *Macrobrachium nipponense* (De Haan). aquaculture 547:737531. https://doi.org/10.1016/j.aquaculture.2021.737531.

Yadav S, Dwivedi A, Tripathi A, Tripathi AK (2022a) Therapeutic potential of short-chain fatty acid production by gut microbiota in neurodegenerative disorders. Nutr Res 106:72–84. https://doi.org/10.1016/j.nutres.2022.07.007

Yadav N, Tripathi AK, Parveen A (2022b) PLGA-quercetin nanoformulation inhibits cancer progression via mitochondrial dependent caspase-3, 7 and independent FoxO1 activation with concomitant PI3K/AKT suppression. Pharmaceutics 14:1326. https://doi.org/10.3390/pharmaceutics14071326

Yan T, Zhang Z, Li D (2020) NGF receptors and PI3K/AKT pathway involved in glucose fluctuation-induced damage to neurons and α-lipoic acid treatment. BMC Neurosci 21:38. https://doi.org/10.1186/s12868-020-00588-y

Yang JK, Feng Y, Yuan MY, Yuan SY, Fu HJ, Wu BY, Sun GZ, Yang GR, Zhang XL, Wang L, Xu X (2006) Plasma glucose levels and diabetes are independent predictors for mortality and morbidity in patients with SARS. Diabet Med 23:623–628. https://doi.org/10.1111/j.1464-5491.2006.01861.x

Yıldırım Baş F, Bayram D, Arslan B, Armağan I, Yeşilot Ş, Çiçek E, Yorgancıgil E (2017) Effect of alpha lipoic acid on smoking-induced skin damage. Cutan Ocul Toxicol 36:67–73. https://doi.org/10.3109/15569527.2016.1154069

Zhao G, Hu C, Xue Y (2018) *In vitro* evaluation of chitosan-coated liposome containing both coenzyme Q10 and alpha-lipoic acid: cytotoxicity, antioxidant activity, and antimicrobial activity. J Cosmet Dermatol 17:258–262. https://doi.org/10.1111/jocd.12369

Zhang J, McCullough PA (2016) Lipoic acid in the prevention of acute kidney injury. Nephron 134:133–140. https://doi.org/10.1159/000448666

Ziegler D, Low PA, Freeman R, Tritschler H, Vinik AI (2016) Predictors of improvement and progression of diabetic polyneuropathy following treatment with α-lipoic acid for 4 years in the NATHAN 1 trial. J Diabetes Complications 30:350–356. https://doi.org/10.1016/j.jdiacomp.2015.10.018